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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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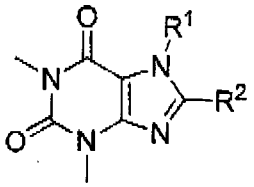
(54) **Title**: SUBSTITUTED XANTHINES AND METHODS OF USE THEREOF

(57) **Abstract**: Compounds, compositions and methods are described for inhibiting the TRPC5 ion channel and disorders related to TRPC5.

AMENDED CLAIMS
received by the International Bureau on 24 November 2014 (24.11.2014)

1. A compound of Formula I:



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1-4 R^3;

R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, halo, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 heteroalkyl, C_6-C_{10} aryloxy, C_7-C_{16} arylalkoxy, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, -C(O)-, -S-, -S-C_1-C_6 alkyl, -S(O)-, -$S(O)_2$-, -O-, heterocycloalkyl, heteroaryl, sulfonamidyl, amido, urea, sulfonylurea, acyl, nitro, cyano, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 heteroalkyl, C_6-C_{10} aryloxy, C_7-C_{16} arylalkoxy, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, -S-, -S-C_1-C_6 alkyl, -S(O)-, -$S(O)_2$-, heterocycloalkyl, heteroaryl, sulfonamidyl, amido, urea, sulfonylurea, acyl, is optionally substituted with 1-3 R^3;

each R^3 is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, halo, C_1-C_6 haloalkoxy, hydroxyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, cyano, nitro, amido, -S-, -$S(O)_2$-, -C(O)-, -C(O)O-C_1-C_6 alkyl, -C(O)-C_1-C_6 alkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, phenyl, or naphthyl, wherein each of C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, amido, -S-, -$S(O)_2$-, -C(O)-, -C(O)O-C_1-C_6 alkyl, -C(O)-C_1-C_6 alkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, phenyl, or naphthyl is optionally substituted with 1-3 R^4; and

each R^4 is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, heterocycloalkyl, C_6-C_{10} aryl, heteroaryl, C_4-C_{10} cycloalkylalkyl, heterocycloalkylalkyl, C_7-C_{16} arylalkyl, heteroaryl-C_1-C_6 alkyl, halo, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_6-C_{10} aryloxy, C_7-C_{16} arylalkoxy, C_2-C_8 alkoxyalkoxyl, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, -S-, -S-C_1-C_6 alkyl, -$S(O)_2$-C_1-C_6 alkyl, sulfonamidyl, amido, urea, sulfonylurea, acyl, -C(O)-C_6-C_{10} aryl, -NHC(O)-C_6-C_{10} aryl, -C(O)NH-C_6-C_{10} aryl, -C(O)OH, -C(O)O-C_1-C_6 alkyl, -C(O)-C_1-C_6 alkyl, acyl, nitro, or cyano.

2. The compound according to claim 1, wherein R^1 is C_1-C_6 alkyl, optionally substituted with 1-4 R^3.

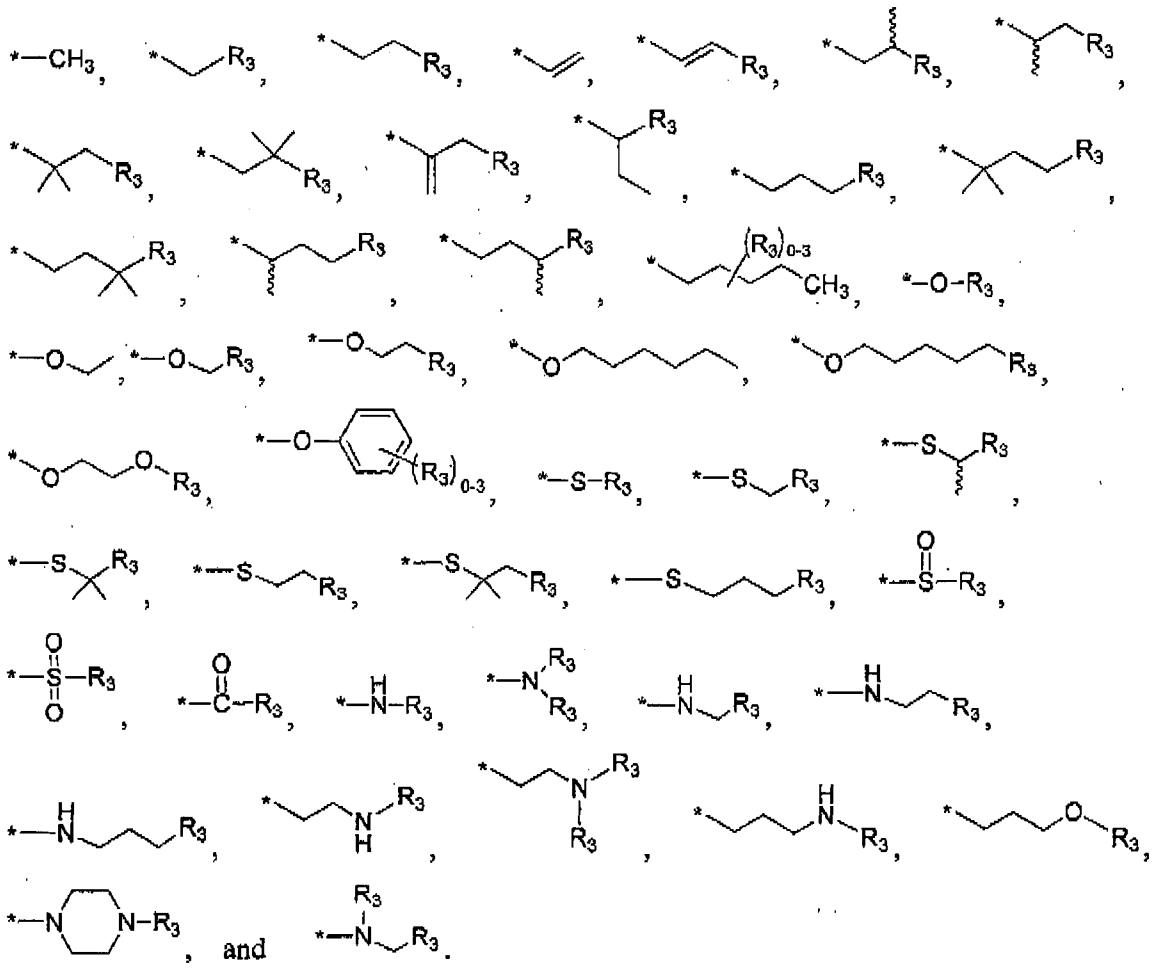
3. The compound according to claim 1, wherein R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, C_1-C_6 heteroalkyl, C_6-C_{10} aryloxy, C_7-C_{16} arylalkoxy, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, -C(O)-, -S-, -S-C_1-C_6 alkyl, -S(O)-, -$S(O)_2$-, -O-, or heterocycloalkyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, C_1-C_6 heteroalkyl, C_6-C_{10} aryloxy, C_7-C_{16} arylalkoxy, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, -S-, -S-C_1-C_6 alkyl, -S(O)-, -$S(O)_2$-, or heterocycloalkyl is optionally substituted with 1-3 R^3.

4. The compound according to claim 3, wherein each R^3 is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, halo, C_1-C_6 haloalkoxy, hydroxyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, cyano, amido, -C(O)-, -C(O)O-C_1-C_6 alkyl, -C(O)-C_1-C_6 alkyl, heterocycloalkyl, phenyl, or napthyl, wherein each of C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkoxy, hydroxyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, amido, -C(O)-, -C(O)O-C_1-C_6 alkyl, -C(O)-C_1-C_6 alkyl, heterocycloalkyl, phenyl, or napthyl is optionally substituted with 1-3 R^4.

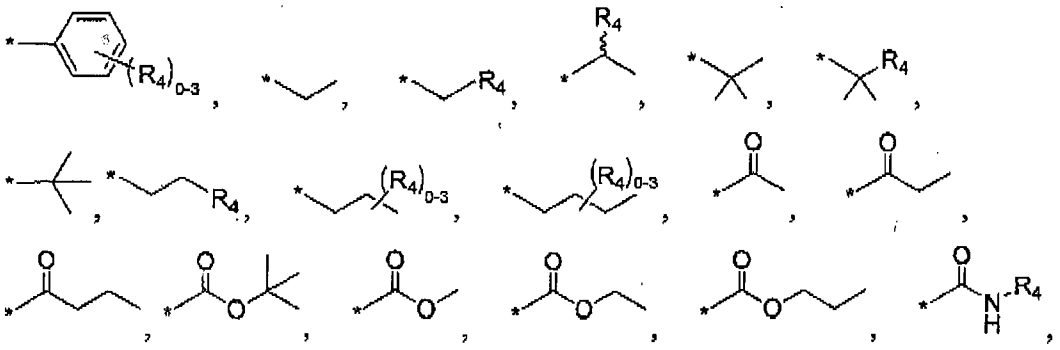
5. The compound according to claim 4, wherein each R^4 is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, heterocycloalkyl, C_6-C_{10} aryl, heteroaryl, C_4-C_{10} cycloalkylalkyl, heterocycloalkylalkyl, heteroaryl-C_1-C_6 alkyl, halo, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, amino, C_1-C_6 alkylamino, C_2-C_{12} dialkylamino, amido, -C(O)O-C_1-C_6 alkyl, -C(O)-C_1-C_6 alkyl, or cyano.

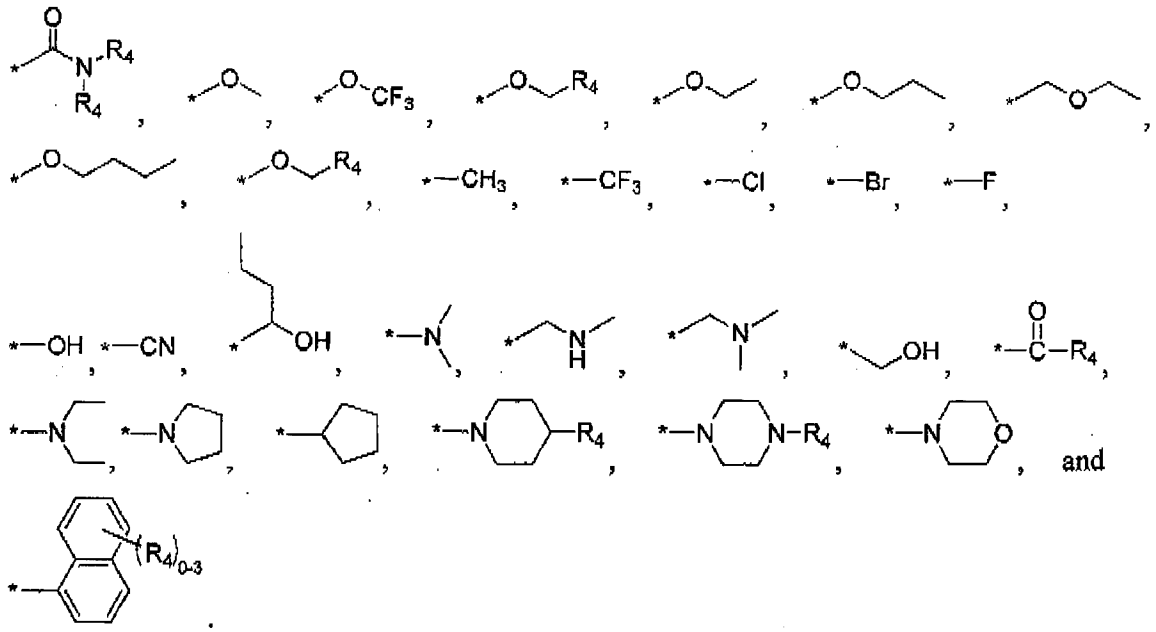
6. The compound according to claim 1, wherein R^1 is selected from the group consisting of:

7. The compound according to claim 1, wherein R^2 is selected from the group consisting of:

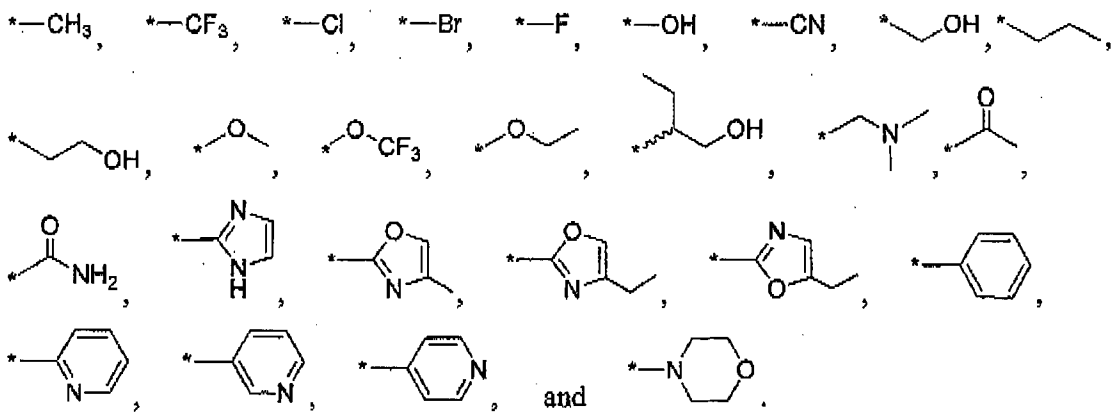


8. The compound according to claim 1, wherein each R^3 is independently selected from the group consisting of:



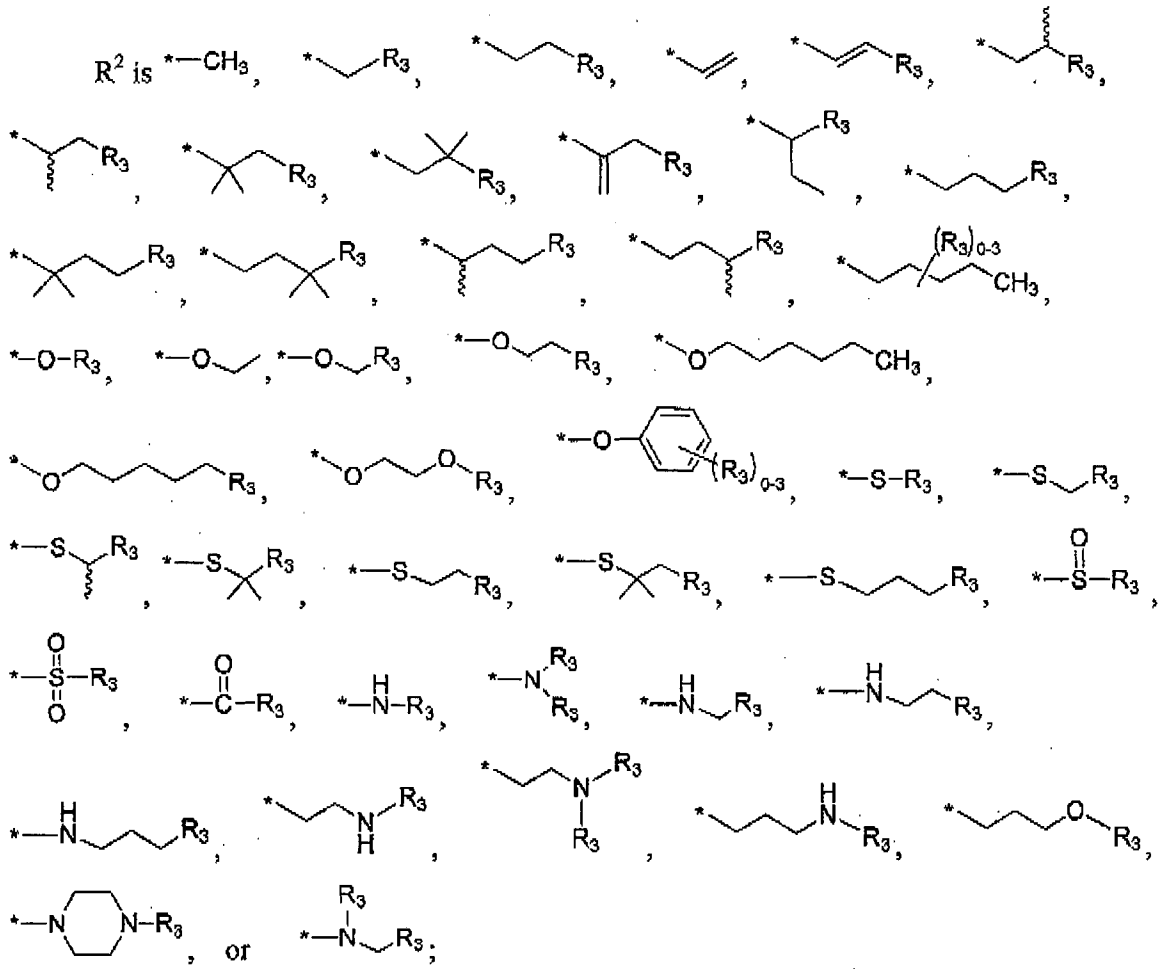


9. The compound according to claim 1, wherein each R^4 is independently selected from the group consisting of:

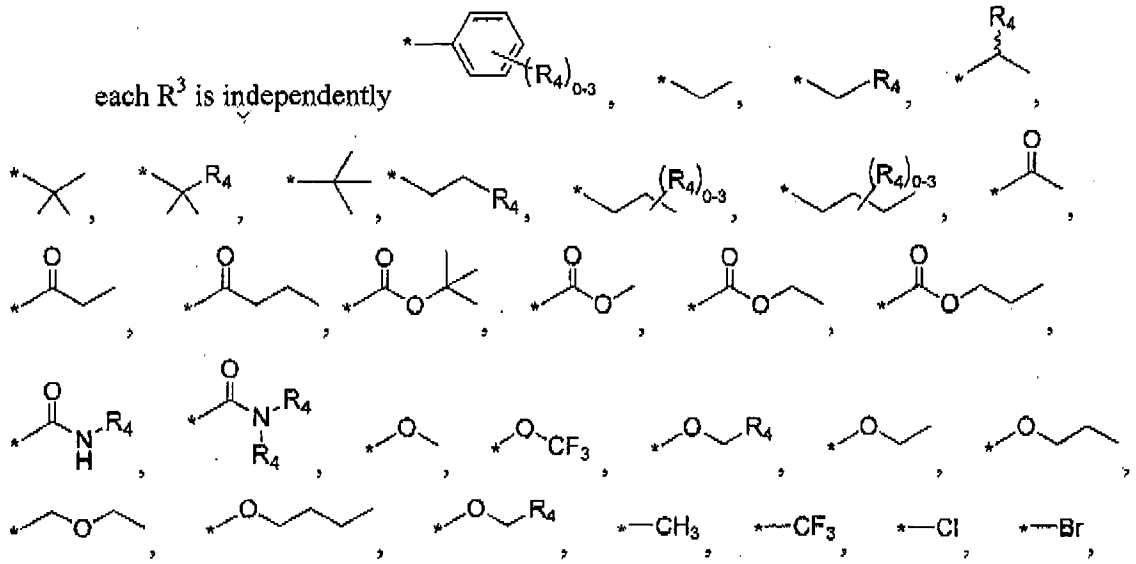


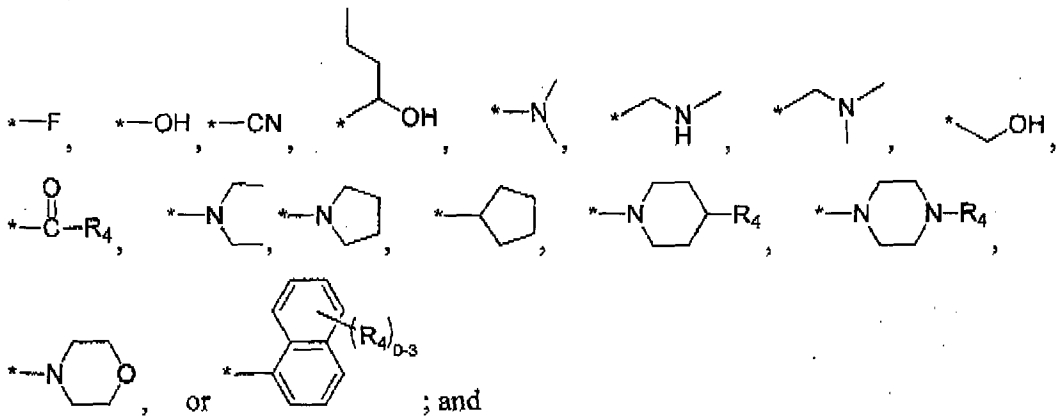
10. The compound according to claim 1, wherein:

R^1 is  ;



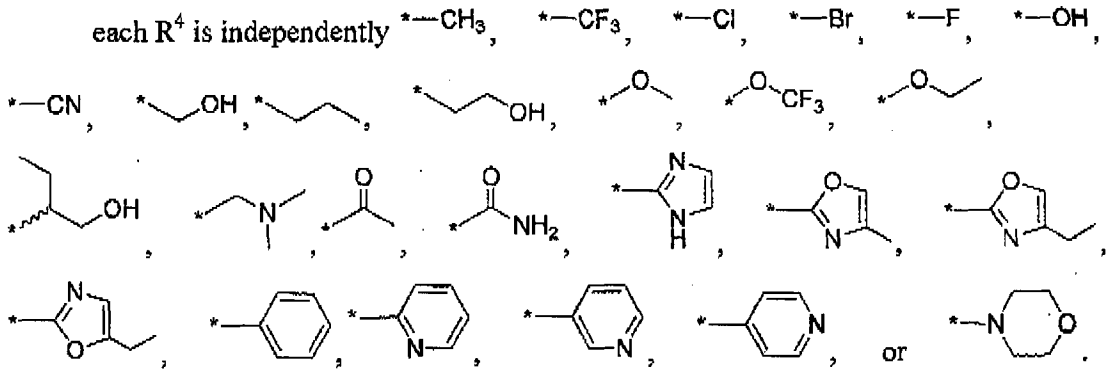
each R^3 is independently



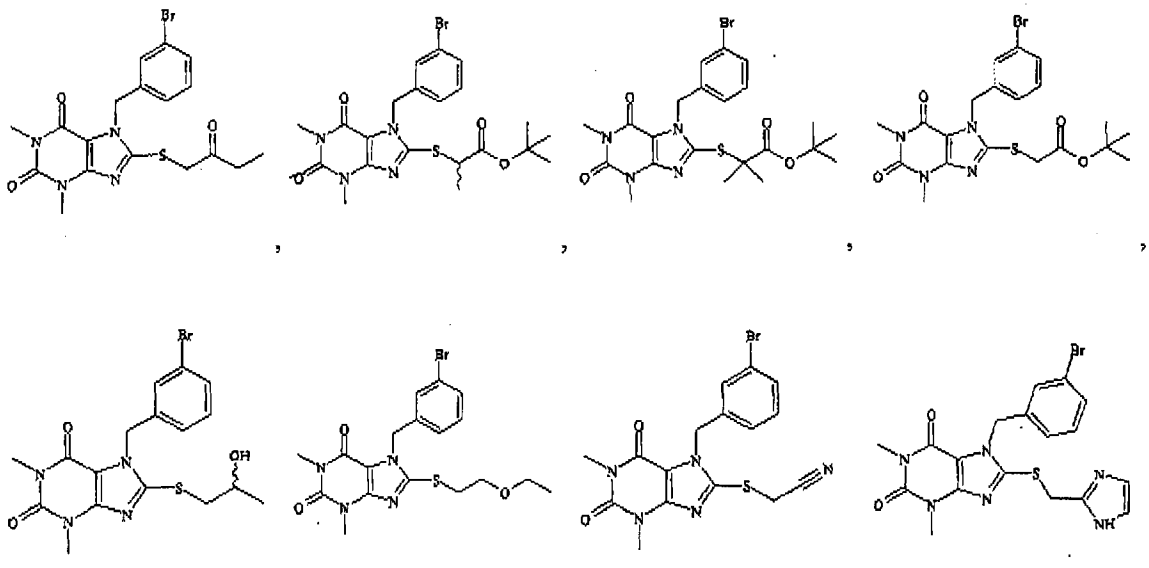


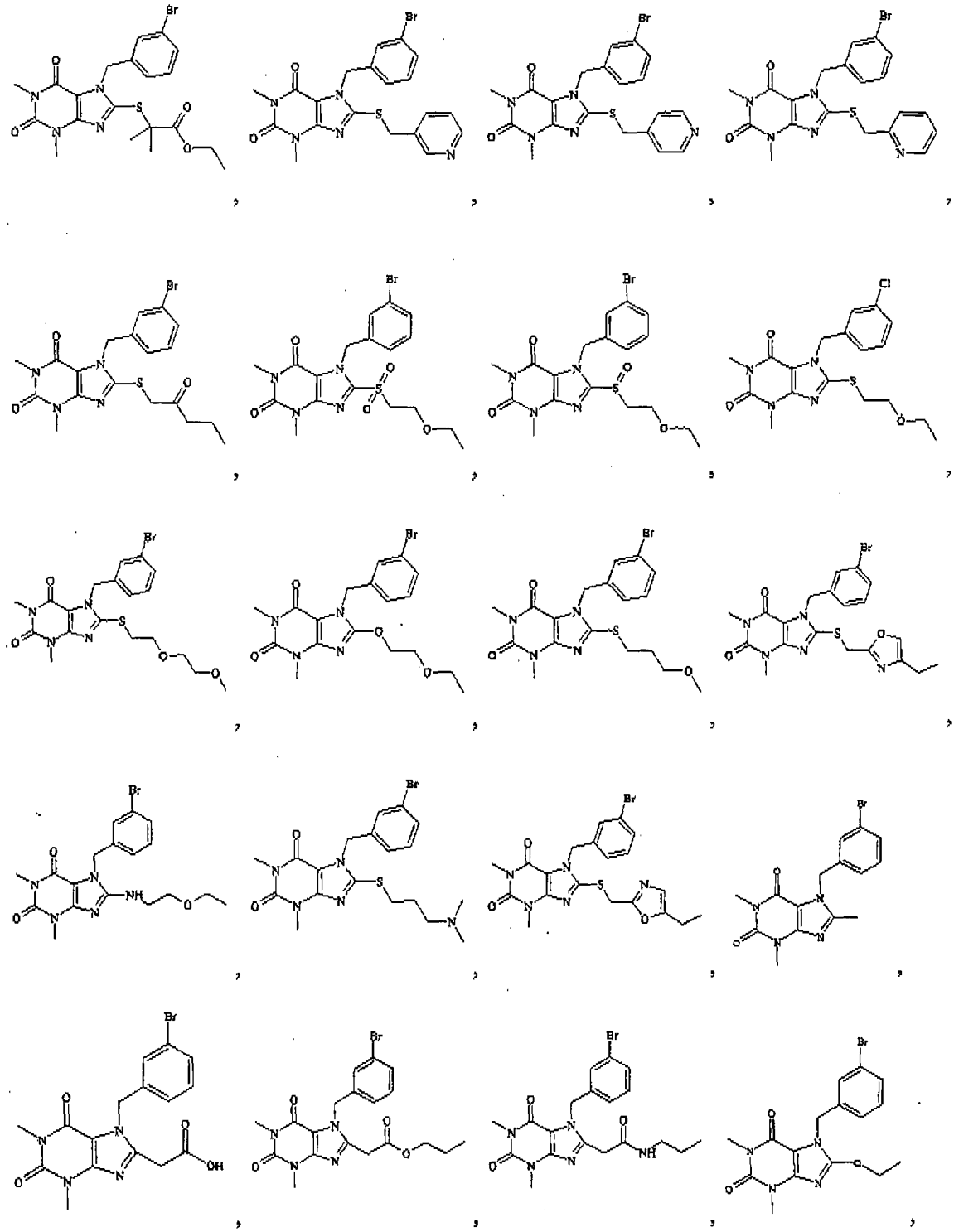
; and

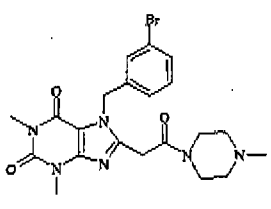
each R^4 is independently



11. The compound according to any of the preceding claims, wherein the compound is selected from the group consisting of:



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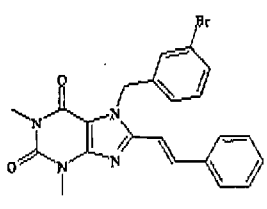
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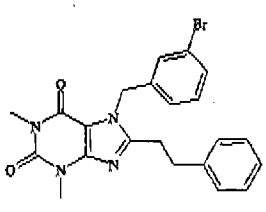
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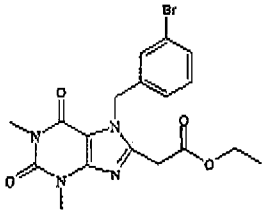
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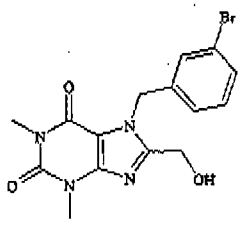
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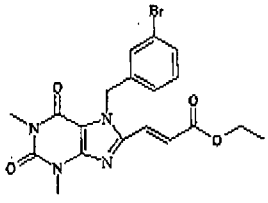
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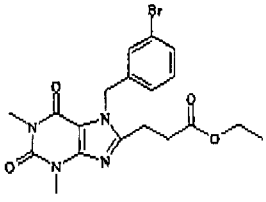
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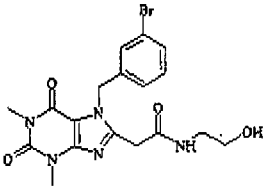
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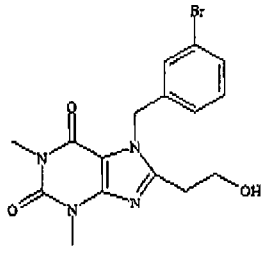
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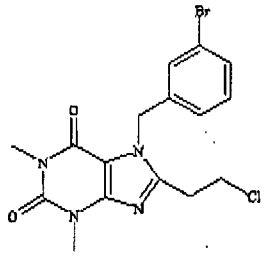
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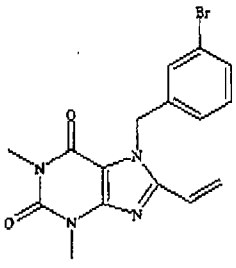
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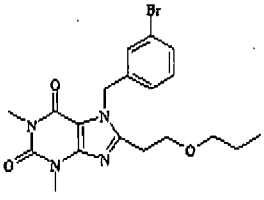
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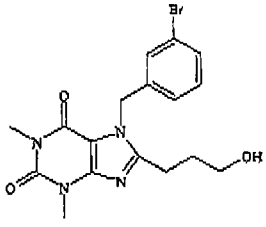
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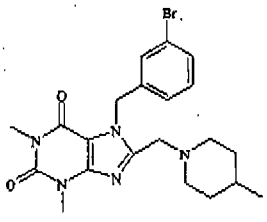
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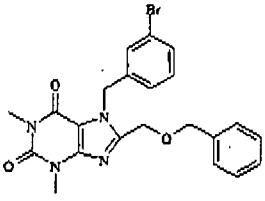
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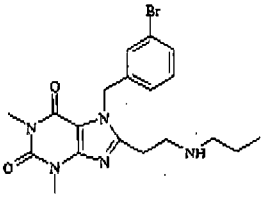
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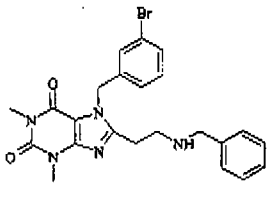
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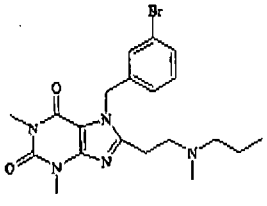
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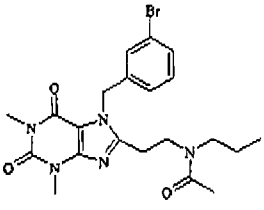
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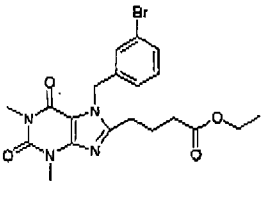
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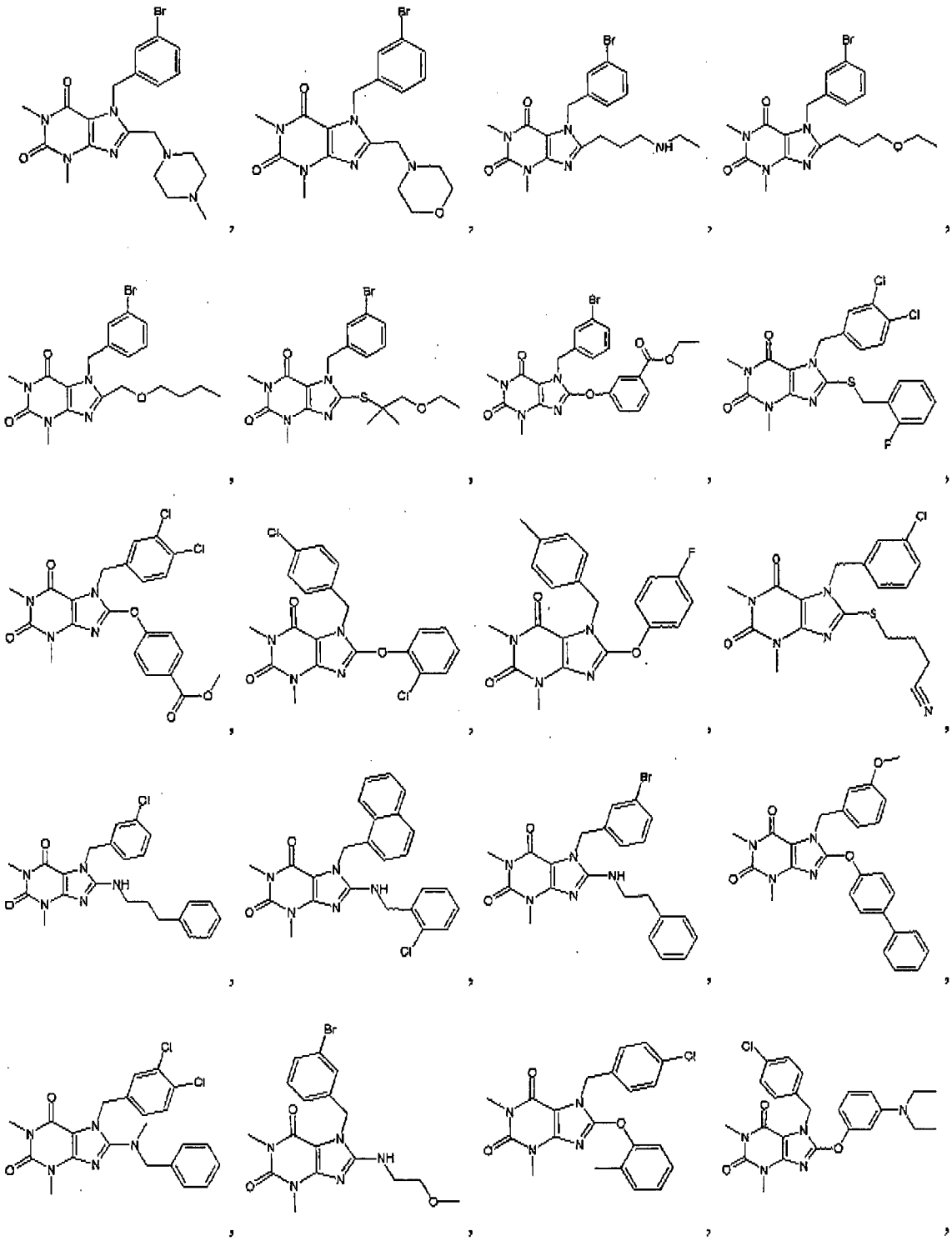
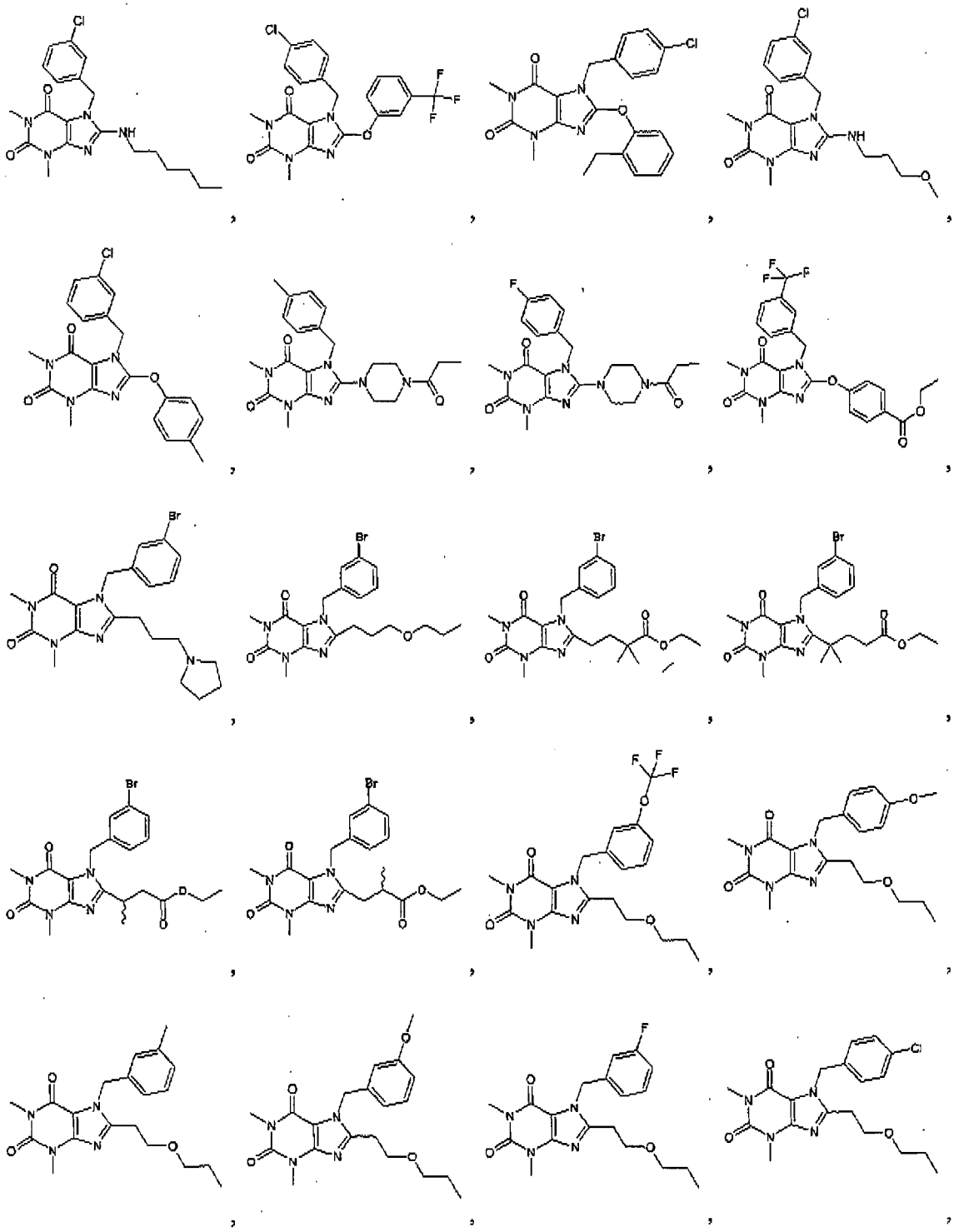
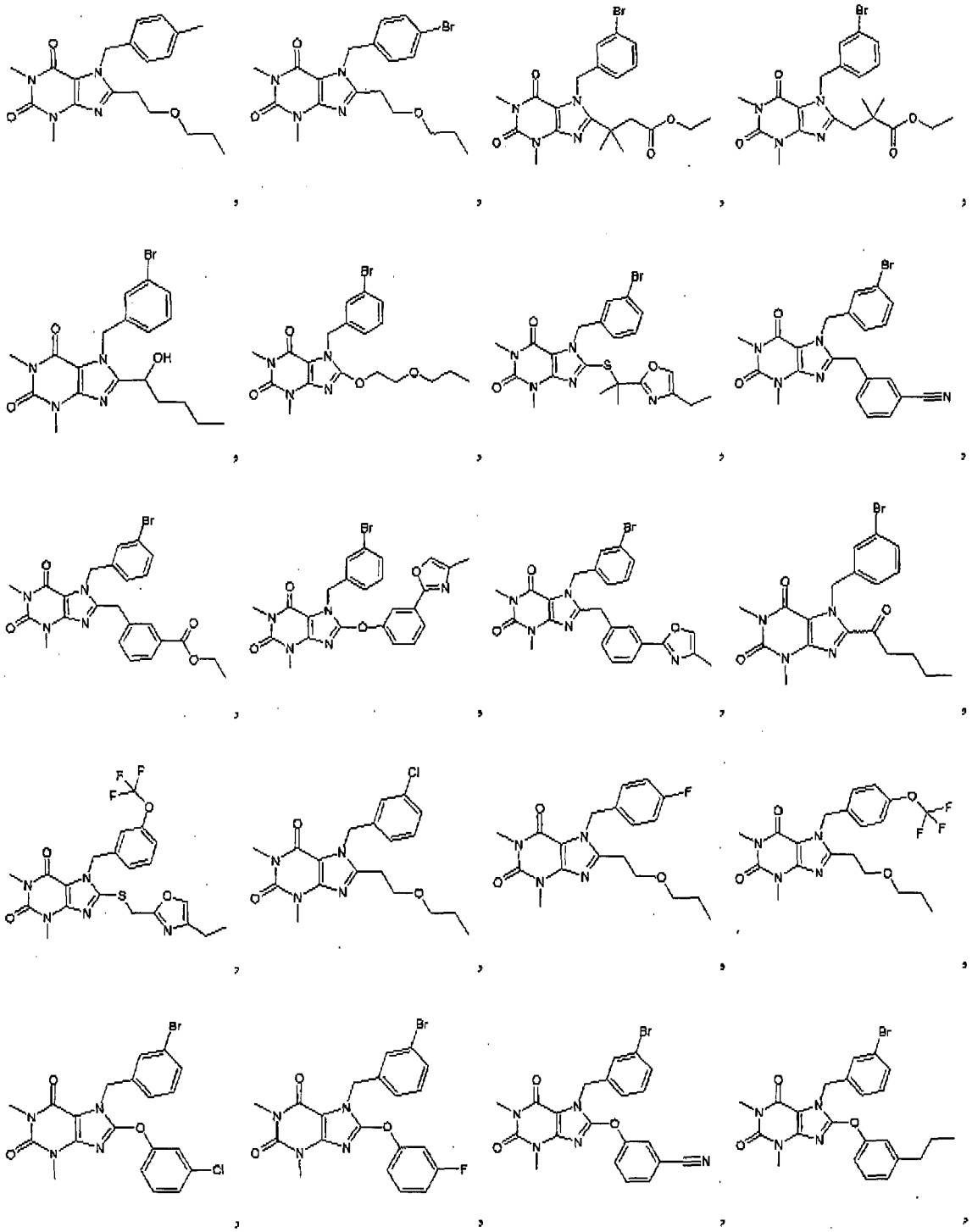
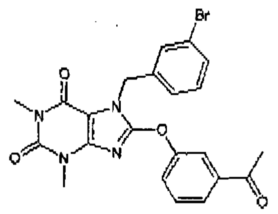
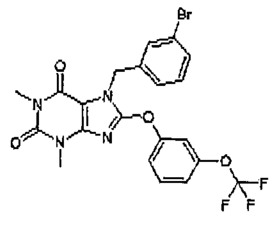
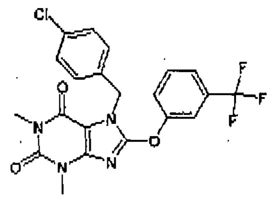
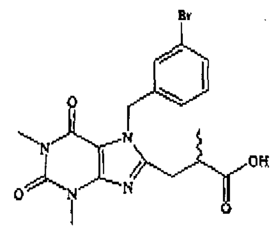
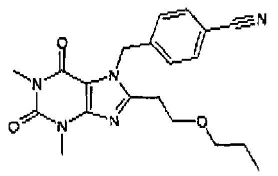
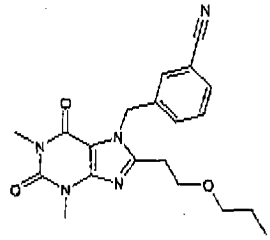
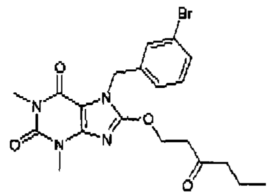
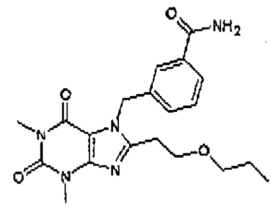
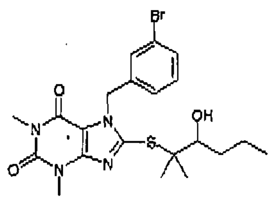
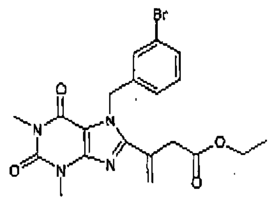
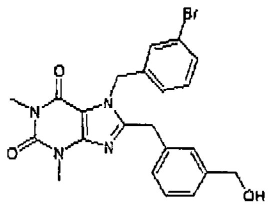
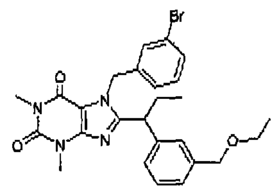


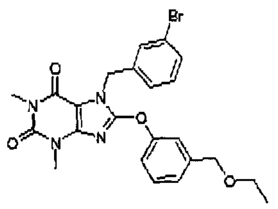
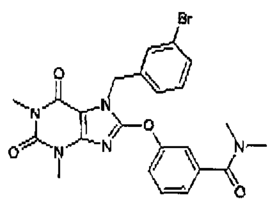
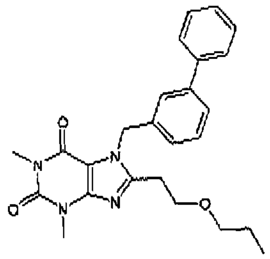
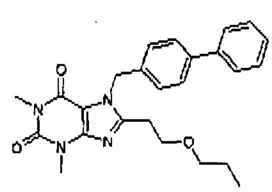


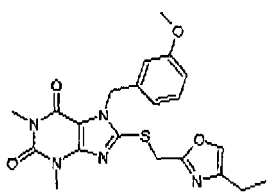
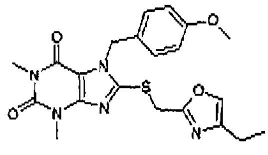
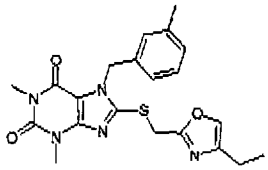
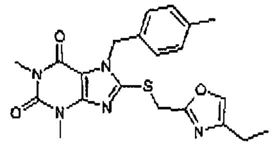


 ,
 ,
 ,
 ,

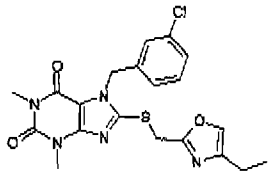
 ,
 ,
 ,
 ,

 ,
 ,
 ,
 ,

 ,
 ,
 ,
 ,

 ,
 ,
 ,
 ,

AMENDED SHEET (ARTICLE 19)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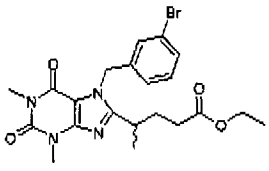
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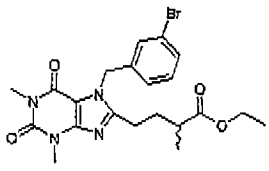
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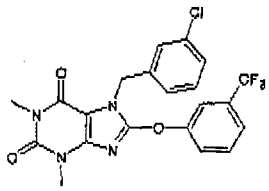
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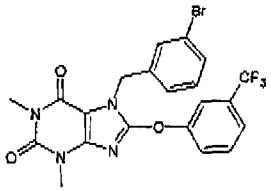
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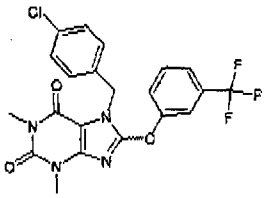
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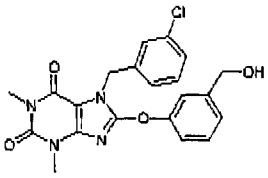
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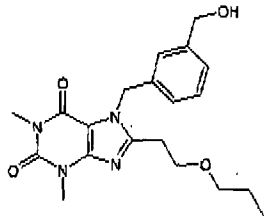
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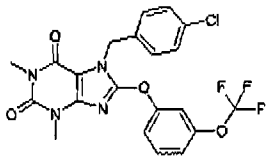
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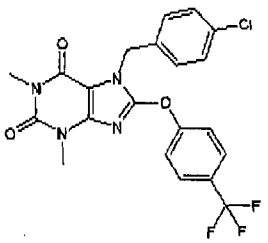
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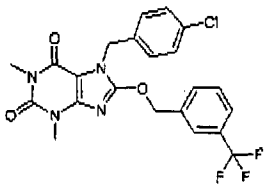
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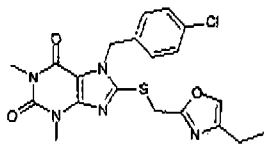
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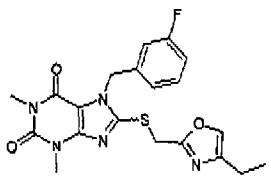
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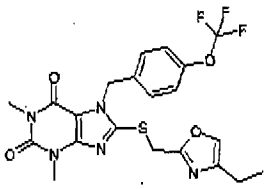
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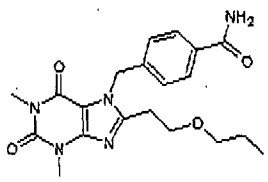
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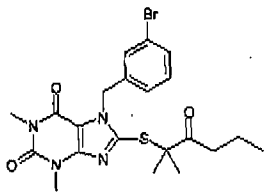
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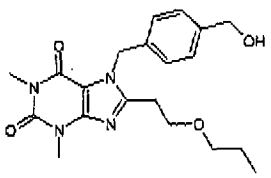
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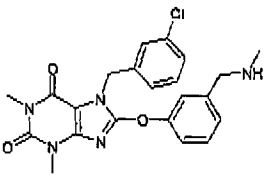
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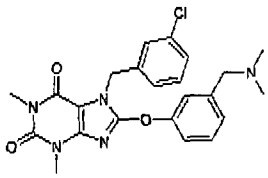
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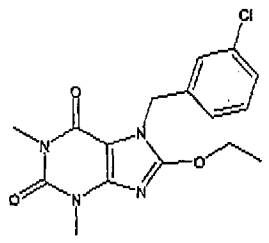
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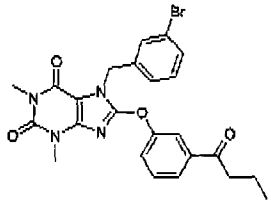
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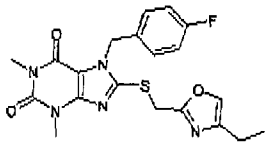
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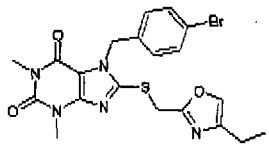
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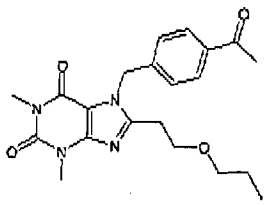
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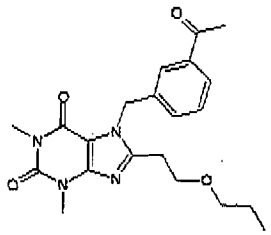
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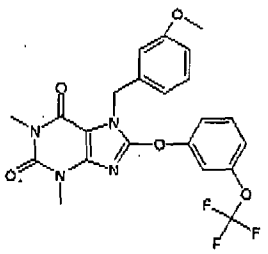
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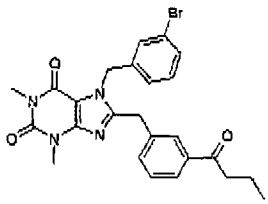
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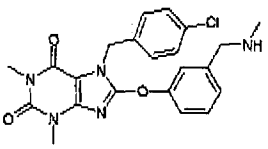
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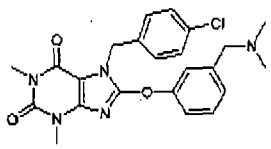
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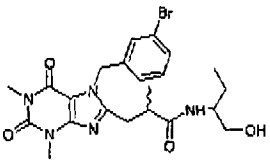
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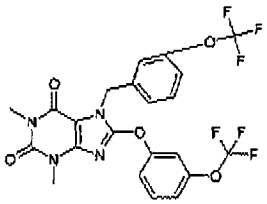
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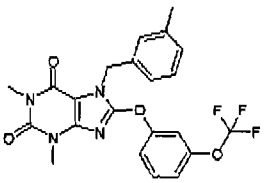
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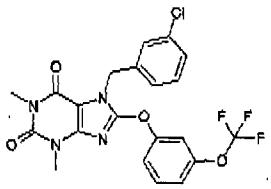
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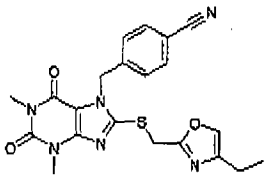
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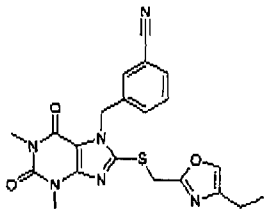
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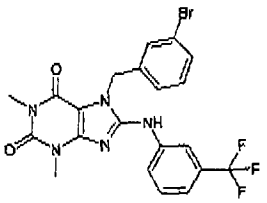
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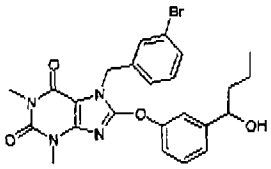
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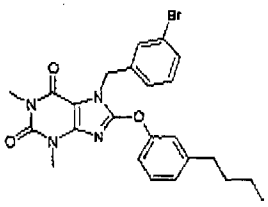
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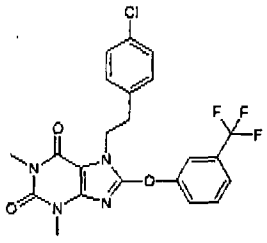
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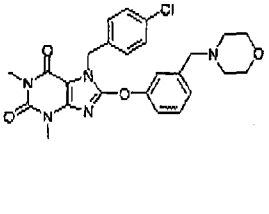

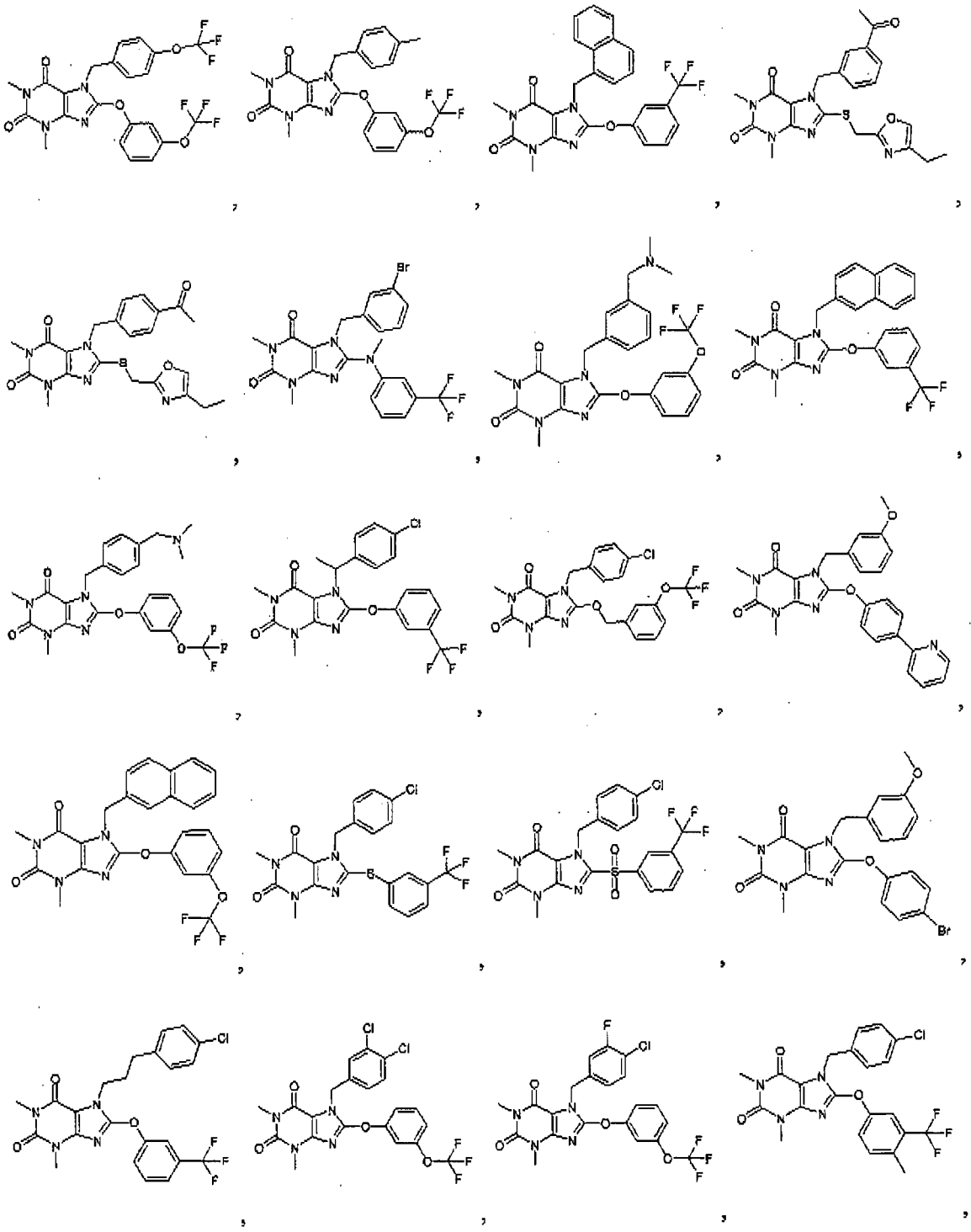

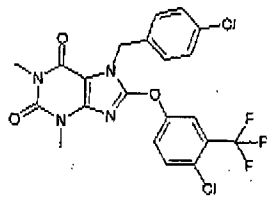
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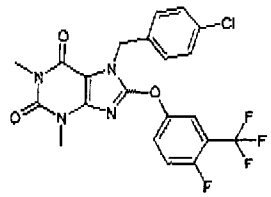
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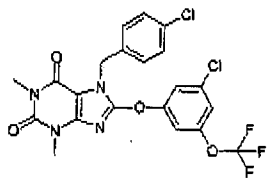
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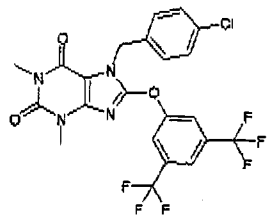
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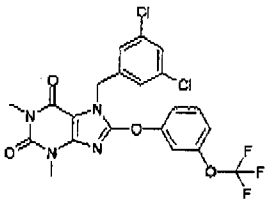
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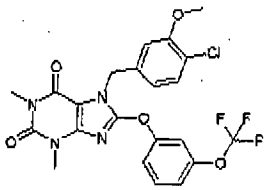
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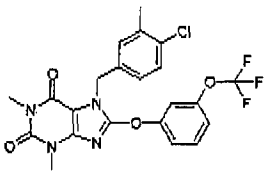
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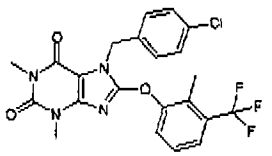
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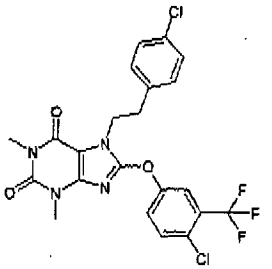
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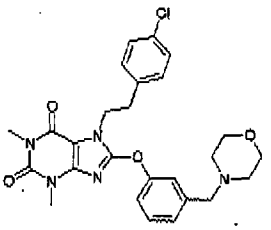
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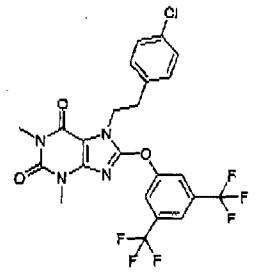
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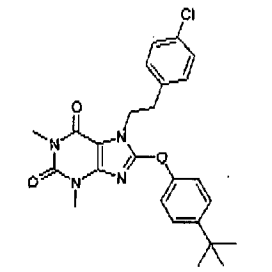
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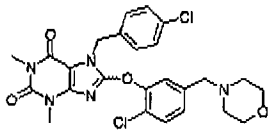
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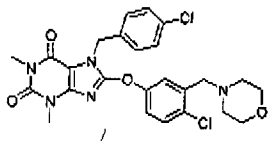
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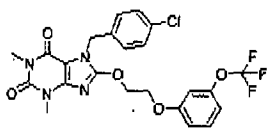
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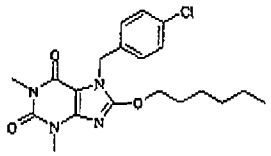
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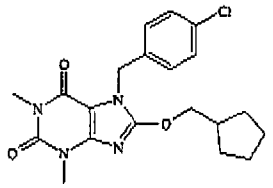
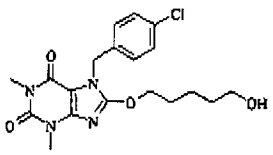
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