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Synthesis and Biological Activity of Novel Thiazolidinediones

C. Prabhakar[†], G. Madhusudhan[†], K. Sahadev[†], Ch. Maheedhara Reddy[†], M.R. Sarma[†], G. Om Reddy[†*], R. Chakrabarti[‡], C. Seshagiri Rao[‡], T. Dileep Kumar[‡] and R. Rajagopalan[‡]

[†]*Department of Process Research and Development,* [‡]*Department of Pharmacology*

Dr. Reddy's Research Foundation, Bollaram Road, Miyapur, Hyderabad - 500 050, India.

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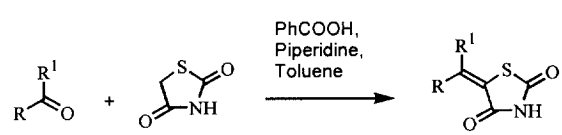
Abstract:

Novel compounds having a dual pharmacophore were synthesised and evaluated for their insulin sensitiser and anti-inflammatory properties in different animal models.

Keywords: Thiazolidinedione; Insulin sensitiser; Anti-inflammatory; Biological activity; Animal models.

Combination of two active pharmacophores into one molecule is one of the novel drug designing techniques used in drug discovery programme [1]. In this communication, we report our early attempts to design and evaluate some of the novel molecules for antidiabetic and antiinflammatory activities. With the recent increased interest in the above area [2,3], search for such potential drugs has been in the forefront of pharmaceutical sciences. In this series, we have combined two active pharmacophores, namely a thiazolidinedione of antidiabetic drugs like troglitazone and a methoxy naphthyl moiety of nabumetone, which is under clinical practice for the treatment on inflammatory disease. Of particular interest in this context is a phase-II antidiabetic candidate, MCC-555 developed by Mitsubishi [4], which exhibits interesting antidiabetic activity along with a marginal antiinflammatory activity (cf. table-1).

Scheme 1



1

An interesting feature of this class of compounds is that they can be retrosynthetically cleaved into two motifs - of which one part, the alkoxy naphthyl motif, resembles an antiinflammatory drug - nabumetone, while the other part, the thiazolidinedione motif is a pharmacophore of the insulin sensitiser drug - troglitazone, which has recently been launched in the Japanese and US markets. Nabumetone produces an active metabolite 6-MNA [5]

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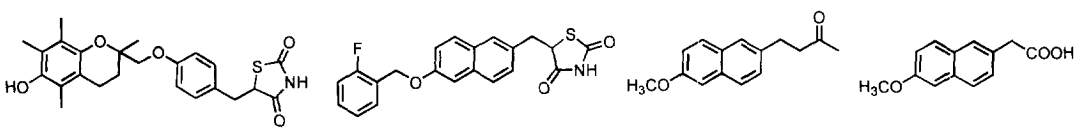
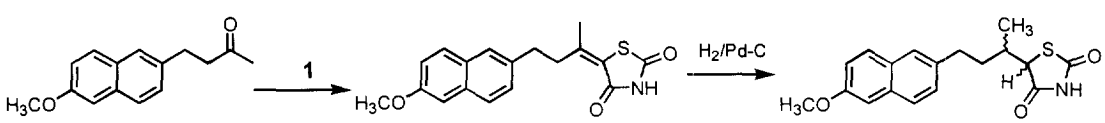
and the same is expected to be released slowly in most of the compounds that are discussed in this communication. The structural similarities between MCC-555 and the compounds described in this communication are very striking. MCC-555 is a 6-(2-flourobenzyloxy)-2-naphthyl derivative of thiazolidine-2,4-dione, which is very similar to the compounds discussed in the present communication, wherein 6-methoxy-2-naphthyl derivatives are described. Spacers with varying carbon chain length have been introduced. Considering the structure-activity relations, it is reasonable to expect similar biological activity for these molecules, when compared with MCC-555 (cf. table-1). Thiophene [6] and furan [7] being two of the most commonly seen moeities in pharmaceutical molecules and an attempt is made to incorporate these two motifs, as well, in our model compounds.



Troglitazone **MCC-555** **Nabumetone** **6-MNA**

The reaction of nabumetone with 2,4-thiazolidinedione **1** under the standard Knoevenagel reaction conditions[1] led to the formation of the unsaturated mixture of E & Z compounds represented by **2**. Despite several meticulous attempts, the two isomers could not be separated. Hence, the mixture was hydrogenated under Pd/C catalysis to give a mixture of diastereoisomers **3** (Scheme 2). Separation of the diastereoisomers was not attempted as our earlier studies with troglitazone proved that the methine proton on the thiazolidinedione ring is prone to rapid epimerisation. However, The activity data (vide infra) showed that the E,Z mixture of the unsaturated compounds (**2**) was more active than the diastereomeric mixture of the saturated compounds (**3**).

Scheme 2



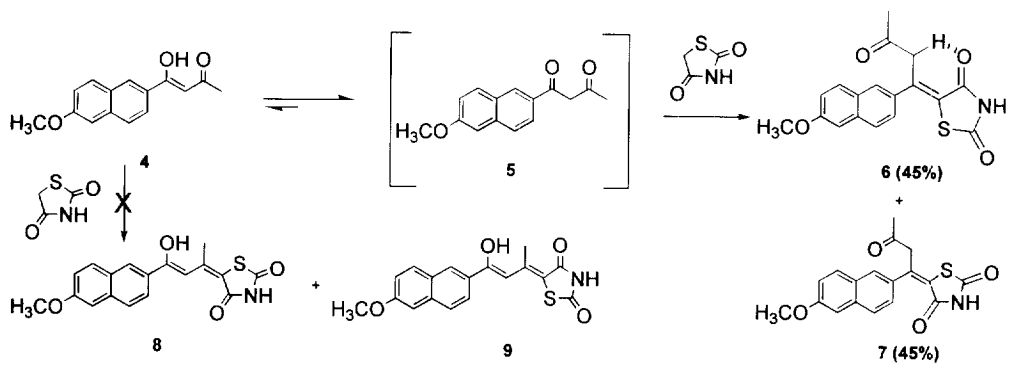
2 (80%) **3 (95%)**

On reacting the enol ketone **4** [8], with thiazolidine-2,4-dione **1**, gave a mixture of E & Z compounds, as expected, but the obtained compounds, **6** and **7**, were found to be different from the expected compounds, **8** and **9**. However, in this instance, separation of these two compounds was reasonably straightforward. The mixture was stirred in cold dichloromethane and the undissolved solid was filtered which was found to be the Z-isomer **6** while concentration of the filtrate gave the E-isomer **7**. Concerning the assignment of the two isomers **6** and **7**, IR and Mass spectral data has been used. In compound **6**, there exists a possibility of C—H---O interaction

[1] General Procedure: The ketone (0.5 M), 2,4-thiazolidinedione (0.5 M), benzoic acid (0.05 M), piperidine (0.05 M) and toluene (250 ml) are mixed and refluxed for a period of 5-15 hours with azeotropic removal of water. After, the completion of the reaction as judged by TLC, the solvent is removed under reduced pressure and the product is purified by chromatography and/or recrystallisation.

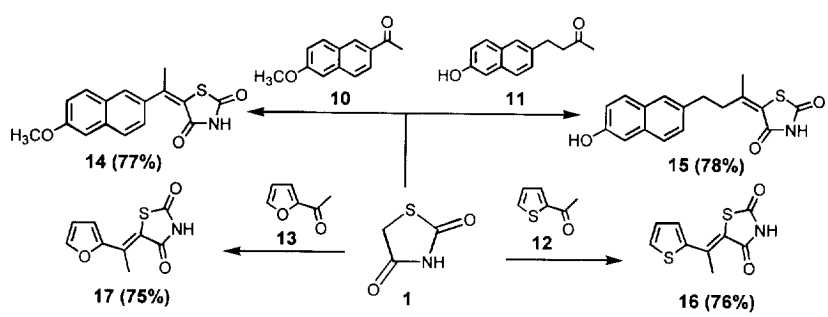
between the γ-hydrogen and the carbonyl oxygen of the thiazolidinedione, as shown in scheme-3. Hence, the carbonyl of thiazolidinedione in **6**, shifts by ~25 cm^{-1} to lower frequency (1706 cm^{-1}) compared to compound **7** (1733 cm^{-1}) wherein this possibility of C—H---O interaction does not exist. The intense fragment peak at 298 (M-43, due to loss of acetyl) in the mass spectrum of **6**. The facile loss of acetyl group in the Z-isomer **6** can also be explained by the interaction of γ-hydrogen with the carbonyl oxygen of the thiazolidinedione. The E-isomer **7** also showed the 298 peak in its mass spectrum corresponding to the loss of acetyl group but the fragment was not very intense, supporting the fact that the carbonyl oxygen of thiazolidinedione was not in proximity. Moreover, DEPT spectra showed the presence of one methyl, one methylene and one methine group in the molecule which supports the composition of compounds **6** and **7**.

Scheme 3



Similar reactions of 2,4-thiazolidinedione with acetyl naroline **10** [9], 4-(6-hydroxy-2-naphthyl)-butan-2-one **11**, 2-acetyl thiophene **12** [10] and 2-acetyl furan **13** gave the corresponding unsaturated compounds **14-17** respectively as shown in Scheme 4.

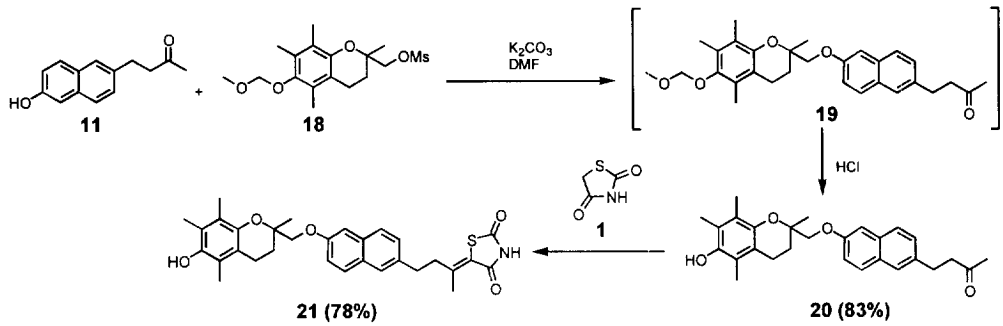
Scheme 4



5-[3-{6-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl-methoxy)-2-naphthyl}-1-methylpropylidine]thiazolidine-2,4-dione **21** was obtained by the reaction of thiazolidinedione with the hydroxyketone **20**. The compound **20** was in turn prepared from the chroman derivative **18** [11] and 4-(6-hydroxy-2-naphthyl)butan-2-one **11** to give

the MOM protected hydroxyketone **19** followed by deprotection in acidic conditions as shown in scheme 5. All the new compounds have been unambiguously characterized by means of various spectral studies [12]. Troglitazone [13], nabumetone [14] and MCC-555 [15] were prepared employing reported procedures.

Scheme-5



Biological Activity Studies:

The screening of antidiabetic activity was carried out in db/db mice of either sex, of 9 weeks age. The compounds were given orally at a dose of 30 mg/Kg. The control animals were treated with vehicle carboxymethylcellulose (0.25% CMC). The blood samples were collected through orbital-sinus in fed state on 0 and 6th days of treatment and analysed for plasma glucose (PG) and triglyceride (TG) levels using commercially available kits. Troglitazone was used as a standard. The anti-inflammatory activity was assesed in carrageenin induced rat paw edema model [16] in Wistar rats of weight range 120-200 g. Nabumetone was used as a standard.

Structure Activity Relationship (SAR):

The following general remarks can be stated regarding SAR of the compounds prepared:

- the unsaturated compound **2** showed better antidiabetic activity both in terms of PG and TG reduction than the saturated compound **3**. However, compound **3** showed marginally better anti-inflammatory activity compared to compound **2**.
- compared to the Z-isomer **6** , the E-isomer **7** showed less biological activity.
- Compound **14** with a methyl group at the α position showed better PG reduction compared to compounds **6** and **7** which have a 2-oxopropyl group at the α position. However, compound **6** showed a better anti-inflammatory action as well, thus exhibiting an interesting dual activity.
- the demethylated compound **15** has completely abolished anti-inflammatory activity, but retained the blood sugar lowering activity
- substitution of naphthyl ring with thiophene as in compound **16**, has completely abolished both the activities while the furan analogue **17** retained the activities to a reasonable extent.

- The naphthyl spacer group in **21** has completely abolished the antidiabetic activity when compared to troglitazone which has a phenyl spacer. However, compound **21** exhibited marginal anti-inflammatory activity.
- To Summarise, compounds **2** and **3** exhibited TG reductions comparable to troglitazone. While compounds **2, 6, 14, 15** and **17** showed interesting PG reduction, compounds **3** and **6** showed reasonably good anti-inflammatory activities. Compounds **7, 16** and **21** did not better the biological profile of the parent molecules. The results are shown in Table-1.

Table 1

Anti-diabetic and Anti-inflammatory Activities

Compound	Dosage mg/Kg	% reduction in PG (n = 4)	% reduction inTG (n = 4)	% reduction in inflammation Dosage: 100 mg/Kg ; (n = 5)
2	30	16	50	10
3	30	8	44	17
6	30	16	NE	25
7	30	NE	NE	7
14	30	26	NE	7
15	30	20	NE	NE
16	30	NE	18	NE
17	30	16	NE	12
21	30	NE	NE	12
MCC-555	30	60	72	18
Troglitazone [17]	200	16	50	3
Nabumetone	20	NE	NE	30

PG: Plasma Glucose; TG: Triglycerides; NE: No Effect

Acknowledgements

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References and Notes

1. Many such examples are known in literature. To cite a few, Acedapsone (antimalarial and antibacterial), Acefylline (diuretic, cardiotonic and bronchodilator), Beclomethasone (antiallergic, antiasthmatic and anti-inflammatory), Benactyzine (antidepressant and anticholinergic), Xylazine (sedative, analgesic and muscle relaxant), Zileuton (antiasthmatic and anti-inflammatory), etc.
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12. **2**: Yield: 80%; HPLC: 99.7%; mp: 162-64 °C; IR (cm^{-1}): 3035, 1735, 1691, 1604, 1328, 1266, 1228, 1169, 1030, 846, 809, 647, 618; ^1H NMR ($CDCl_3$, δ ppm): 8.1 (Br s), 7.0-7.7 (series of m), 3.9 (s), 3.2 (m), 2.95 (m), 2.6 (m), 2.0 (s), 1.6 (s); Mass: 327 (M^+); **3**: Yield: 95%; HPLC: 99.2%; mp: 186-88 °C; IR (cm^{-1}): 3054, 1744, 1684, 1333, 1231, 1154, 1028, 813, 660; ^1H NMR ($CDCl_3$, δ ppm): 7.9 (Br s), 7.7 (m), 7.5 (m), 7.3 (m), 7.1 (m), 4.5 (d), 4.4 (d), 3.9 (s), 2.6-3.0 (series of m), 2.4 (m), 1.8 (m), 1.2 (d), 1.1 (d); Mass: 329 (M^+); **6**: Yield: 45%; HPLC: 99.6%; mp: 200-04 °C; IR (cm^{-1}): 3156, 1706, 1619, 1482, 1389, 1322, 1266, 1201, 1166, 1033, 862, 808, 637; ^1H NMR ($CDCl_3$ +DMSO, δ ppm): 11.9 (Br s), 8.5 (s), 7.8-8.0 (m), 7.2 (m), 4.8 (s), 4.0 (s), 2.1 (s); ^{13}C NMR (DMSO, δ ppm): 195.2, 166.6, 166.0, 159.5, 145.8, 137.0, 131.6, 131.2, 130.3, 129.8, 127.4, 127.1, 124.0, 122.5, 119.5, 106.0, 55.3, 44.1, 25.7; Mass: 341 (M^+), 298 (M-43, due to loss of acetyl); **7**: Yield: 45%; HPLC: 99.5%; mp: 190-01 °C; IR (cm^{-1}): 3009, 1733, 1688, 1618, 1481, 1390, 1328, 1269, 1184, 1163, 1024, 856, 810, 636; ^1H NMR (DMSO, δ ppm): 12.3 (Br s), 8.7 (s), 8.1 (m), 7.45 (s), 7.25 (m), 4.8 (s), 3.95 (s), 2.0 (s); ^{13}C NMR (DMSO, δ ppm): 195.2, 166.7, 166.0, 159.5, 145.8, 137.1, 131.7, 131.2, 129.8, 127.4, 127.1, 124.1, 122.6, 119.6, 106.0, 55.3, 44.1, 25.8; Mass: 341 (M^+), 298 (M-43, due to loss of acetyl); **14**: Yield: 77%; HPLC: 99.1%; mp: 186-88 °C; IR (cm^{-1}): 3214, 1739, 1668, 1599, 1388, 1320, 1272, 1205, 1162, 1026, 847, 761, 685, 641, 561; ^1H NMR ($CDCl_3$, δ ppm): 8.5 (Br s), 7.8 (m), 7.4 (m), 7.1-7.2 (m), 3.95 (s), 2.8 (s); Mass: 299 (M^+); **15**: Yield: 78%; HPLC: 99.0%; mp: 216-19 °C; IR (cm^{-1}): 3351, 3176, 3036, 1730, 1654, 1605, 1325, 1212, 1176, 1146, 872, 772, 653, 617; ^1H NMR ($CDCl_3$+DMSO, δ ppm): 11.4 (Br s), 8.8 (s), 7.0-7.7 (series of m), 3.2 (m), 2.9 (m), 1.95 (s); ^{13}C NMR (DMSO, δ ppm): 166.8, 165.6, 154.9, 152.6, 135.1, 133.2, 128.8, 127.8, 127.3, 126.0, 120.5, 118.6, 108.6, 36.1, 33.6, 24.7; Mass: 313 (M^+); **16**: Yield: 76%; HPLC: 99.3%; mp: 208-10 °C; IR (cm^{-1}): 3005, 1732, 1673, 1544, 1315, 707, 636, 616, 543; ^1H NMR ($CDCl_3$+DMSO, δ ppm): 11.6 (Br s), 7.6 (m), 7.45 (m), 7.2 (m), 2.85 (s); ^{13}C NMR (DMSO, δ ppm): 166.9, 166.8, 142.7, 139.8, 130.9, 130.6, 128.3, 118.7, 20.3; Mass: 225 (M^+); **17**: Yield: 75%; HPLC: 99.3%; mp: 225-27 °C; IR (cm^{-1}): 3010, 1714, 1669, 1572, 1535, 1324, 1303, 1149, 764, 707, 618, 576; ^1H NMR ($CDCl_3$+DMSO, δ ppm): 11.2 (Br s), 7.6 (m), 6.8 (m), 6.5 (m), 2.7 (s); ^{13}C NMR (DMSO, δ ppm): 168.6, 167.4, 152.1, 146.5, 132.9, 116.2, 113.1, 16.4; Mass: 209 (M^+); **21**: Yield: 78%; HPLC: 99.0%; mp: 217-20 °C; IR (cm^{-1}): 3438, 2928, 1722, 1680, 1607, 1455, 1332, 1256, 1227, 1161, 1119, 853, 647, 614; ^1H NMR ($CDCl_3$ + DMSO, δ ppm): 11.3 (Br s), 7.0-7.7 (series of m), 5.9 (br s), 4.0 (m), 3.2 (m), 2.9 (m), 2.6 (m), 2.1 (m), 2.1 (s), 2.0 (s), 1.95 (s), 1.5 (s); Mass: 531 (M^+).
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