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Bioorganic & Medicinal Chemistry Letters 15 (2005) 2115–2117
Bioorganic & Medicinal Chemistry Letters

Synthesis and in vivo antihyperglycemic activity of 5-(1*H*-pyrazol-3-yl)methyl-1*H*-tetrazoles

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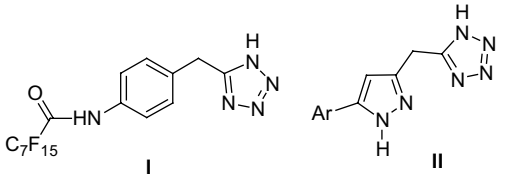
Received 10 January 2005; accepted 9 February 2005
Available online 19 March 2005

Abstract—A series of 5-[(5-aryl-1*H*-pyrazol-3-yl)methyl]-1*H*-tetrazoles **3a**–**h** have been synthesized and evaluated for their in vivo antihyperglycemic activity. Some of the synthesized compounds have shown significant glucose lowering activity in male Sprague–Dawley rats in sucrose loaded model. These compounds were also evaluated for their peroxisome proliferator activated receptor γ agonistic property, but none of them displayed any significant activity.

1. Introduction

Type 2 diabetes is the most common form of diabetes, prevalent in 90–95% diabetics[1] and is characterized by insulin resistance in the liver and peripheral tissues together with a pancreatic β-cell defects.[2] The treatment of type 2 diabetes is currently managed with a combination of exercise, restriction of caloric intake[3] and drug therapy. Sulfonyl ureas are most common oral hypoglycemic agents but some times their major drawback is to produce serious hypoglycemia.[4] Thus, use of nonsulfonyl urea class of compounds are desirable which do not increase insulin secretion but enhance the action of insulin.[5] A series of perfluoro amides (**I**) having 1*H*-1,2,4-tetrazole moiety as an acidic heterocycle have been reported[6] to display highly significant insulin sensitizing property and thereby exhibit potent hypoglycemic activity.

These results prompted us to develop novel and safer hypoglycemic agents with 1*H*-tetrazole moiety (**II**) in their molecular make-up as a nonclassical isosteres of thiazolidinedione class of compounds to explore their insulin sensitizing property.[7–10]



I II

All the synthesized compounds were evaluated as insulin sensitizers and for glucose lowering activity in sucrose loaded model (SLM) in rat.

2. Chemistry

The 5-aryl-3-cyanomethyl-1*H*-pyrazoles (**2**), employed as precursors for the synthesis of 5-(pyrazol-3-yl)-1*H*-tetrazole (**3**) were prepared[11] by the ring transformation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile (**1**) by hydrazine hydrate.

A reaction of 5-aryl-3-cyanomethyl-1*H*-pyrazoles (**2**) with sodium azide and ammonium chloride in DMF afforded 5-(pyrazol-3-yl)-1*H*-tetrazole (**3a**–**h**) in moderate yields (Scheme 1). All the synthesized compounds were characterized[12] by spectroscopic and elemental analyses.

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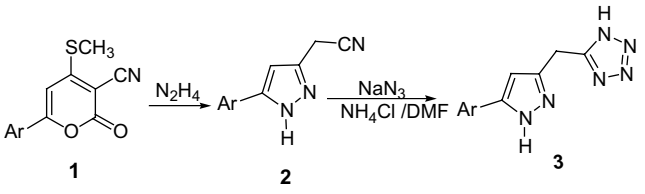
doi:10.1016/j.bmcl.2005.02.060



2,3	Ar
a	C_6H_5
b	4-$SCH_3.C_6H_4$
c	4-$Cl.C_6H_4$
d	4-$Br.C_6H_4$
e	2-Thienyl
f	2-benzofuryl
g	4-$CH_3S(CH_2)_2O.C_6H_4$
h	4-$C_6H_5CH_2(CH_3)N(CH_2)_2O.C_6H_4$
i	4-$C_2H_5S(CH_2)_2O.C_6H_4$
j	4-$C_5H_{11}N(CH_2)_2O.C_6H_4$

Scheme 1.

3. Results and discussion

All the synthesized compounds were initially evaluated by PPAR-trans-activation assay for their agonistic property[13] to assess their insulin sensitizing potential by comparing with a standard drug rosiglitazone, but none of them demonstrated any significant activity.

Further these compounds were assayed for in vivo antihyperglycemic activity in male Sprague–Dawley rat of body weight 160 ± 20 g. The antihyperglycemic activity of the compounds **3a**–**h** was determined at 100 mg/kg dose in sucrose loaded model. Out of eight screened compounds only **3e** and **g** demonstrated 21.4% and 24.6% of blood glucose lowering activity, respectively, while **3d** and **h** lowered the blood glucose level by 18.0%. Rest of the compounds had insignificant activity (see Table 1).

3.1. Sucrose-loaded model

Overnight fasted male Sprague–Dawley rats were used for sucrose loaded experiment. Blood was collected initially and thereafter test compounds were given to the test group consisting of five rats by oral gavage at a dose of 100 mg/kg body weight. After half an hour post-treatment, a sucrose load of 10 mg/kg body weight was given to each rat. Blood was collected at 30, 60, 90 and 120 min post sucrose load. The % fall in blood glucose level was calculated according to AUC method.

Table 1. In vivo antihyperglycemic activity of 1-*H*-tetrazole **3a**–**h** in sucrose loaded model

3	% Blood glucose lowering[a]
a	10.6
b	6.06
c	10.8
d	18.0
e	21.4
f	6.20
g	24.6
h	18.0
Metformin	12.9

[a] Values are means of three experiments tested at 100 mg/kg dose.

It is evident from the screening results of compounds **3b**–**d** that the blood glucose lowering activity increases with decrease in electronegativity of substituent present at position 4 of the aryl ring. A compound without substituent at position 4 in aryl ring of **3a** reduces the blood glucose level almost equal to the 4-chloro substituted phenyl ring **3c**. Among all the screened compounds **3g** was most potent, and decreased the blood glucose level to the tune of 24.6%. The two compounds **3d** and **h** were found almost equally active. An increase in the bulk of the substituent at position 4 of the phenyl ring in **3h** compared to **3g** decreased the activity profile of former. Based on the screening results of synthesized compounds it was concluded that it is worth synthesizing the 1*H*-tetrazole derivatives for lead generation and to explore their potential as antidiabetic agents.

Acknowledgements

V. J. Ram and R. Pratap are thankful to ICMR for financial support.

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12. Synthetic procedure and characterization data for the prepared compounds. General procedure for the synthesis of **2**: A mixture of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-

3-carbonitrile (1 mmol) and hydrazine hydrate (1.5 mmol) in pyridine was reflux for 2.5 h. The solvent was removed under reduced pressure and residue was taken in chloroform and washed with water. The chloroform layer was separated and dried over anhyd sodium sulfate. The dried solution was evaporated to dryness and crude product purified by Si gel column chromatography using 5% ethyl acetate in chloroform as eluent. Compounds **2a**–**f** were synthesized and reported by us.[14] Compound **2g**: yield: 50%; mp: 160–161 °C; MS (FAB): 274 (M^++1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.23 (s, 3H, SCH_3), 2.87–2.94 (t, 2H, J = 6.74 Hz, CH_2), 3.79 (s, 2H, CH_2), 4.16–4.23 (t, 2H, J = 6.74 Hz, CH_2), 6.48 (s, 1H, ArH), 6.95–6.99 (d, 2H, J = 8.80 Hz, ArH), 7.46–7.50 (d, 2H, J = 8.74 Hz, ArH); Anal. Calcd for $C_{14}H_{15}N_3OS$: C, 61.51; H, 5.53; N, 15.37; S, 11.73. Found: C, 61.59; H, 5.49; N, 15.27; S, 11.77. Compound **2h**: yield: 52%; mp: 80–81 °C; MS (FAB): 347 (M^++1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.36 (s, 3H, NCH_3), 2.83–2.89 (t, 2H, J = 5.80 Hz, CH_2), 3.6 (s, 2H, $PhCH_2$), 3.79 (s, 2H, CH_2CN), 4.10–4.16 (t, 2H, J = 5.93 Hz, CH_2), 6.48 (s, 1H, ArH), 6.93–6.97 (d, 2H, J = 8.71 Hz, ArH), 7.28–7.34 (m, 5H, ArH), 7.43–7.48 (d, 2H, J = 8.60 Hz, ArH); Anal. Calcd for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 72.77; H, 6.35; N, 16.19. Compound **2i**: yield: 75%; mp: 121 °C; MS (FAB): 288 (M^++1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.2–1.34 (m, 3H, CH_3), 2.64–2.68 (q, 2H, SCH_2), 2.89–2.97 (t, 2H, J = 6.74 Hz, CH_2), 3.79 (s, 2H, CH_2CN), 4.15–4.21 (t, 2H, J = 6.74 Hz, CH_2), 6.48 (s, 1H, ArH), 6.95–6.99 (d, 2H, J = 8.80 Hz, ArH), 7.46–7.50 (d, 2H, J = 8.74 Hz, ArH); Anal. Calcd for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62; S, 11.16. Found: C, 62.59; H, 5.94; N, 14.52; S, 11.23. Compound **2j**: yield: 50%; mp: 60–61 °C; MS (FAB): 311 (M^++1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45–1.67 (m, 6H, $3CH_2$), 2.51–2.56 (t, 4H, $2NCH_2$), 2.70–2.82 (t, 2H, J = 5.92 Hz, CH_2), 3.77 (s, 2H, CH_2), 4.12–4.15 (t, 2H, J = 5.98 Hz, CH_2), 6.46 (s, 1H, ArH), 6.90–6.99 (d, 2H, J = 8.80 Hz, ArH), 7.46–7.50 (d, 2H, J = 8.74 Hz, ArH); Anal. Calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.69; H, 7.13; N, 18.15.

General procedure for synthesis of **3**. These were obtained by heating a mixture of (5-substituted-1*H*-pyrazol-3-yl) acetonitrile **2**, (1 mmol), sodium azide (3 mmol) and ammonium chloride (3 mmol) in DMF at 120 °C for 24 h. Reaction mixture was cooled to room temperature and concentrated under reduced pressure. Solid residue was taken in to water (25 mL) and stirred for half an hour. Solid obtained was filtered, washed with water and finally purified by Si gel column using 10% methanol in chloroform as eluent. Compound **a**: yield: 48%; mp: >250 °C; MS (FAB): 227 (M^++1); IR (neat): ν = 3138, 1589, 1487, 1358, 1264 cm^{-1} ; ^{1}H NMR (DMSO, 200 MHz) δ 4.17 (s, 2H, CH_2), 6.47 (s, 1H, ArH), 7.27 (t, J = 7.2 Hz, 1H, ArH), 7.39 (t, J = 7.5 Hz, 2H, ArH), 7.71 (d, J = 7.5 Hz, 2H, ArH); Anal. Calcd for $C_{11}H_{10}N_6$: C, 58.41; H, 4.42; N, 37.17. Found: C, 58.11; H, 4.61; N, 37.73. Compound **(b)**: yield: 35%; mp: 222–226 °C; MS (FAB): 274 (M^++1); IR (neat): ν = 3140, 1589, 1487, 1360, 1266 cm^{-1}; ^{1}H NMR (DMSO, 200 MHz): δ 2.30 (s, 3H, SCH_3), 4.11 (s, 2H, CH_2), 6.34 (s, 1H, ArH), 7.10 (d, J = 8.38 Hz, 2H, ArH), 7.47 (d, J = 8.38 Hz, 2H, ArH); Anal. Calcd for $C_{11}H_9FN_6$: C, 54.10; H, 3.71; N, 34.41. Found: C, 54.20; H, 3.75; N, 34.46. Compound **(c)**: yield: 33%; mp: >250 °C; MS (FAB): 261 (M^++1); IR (neat): ν = 3139, 1587, 1487, 1361, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.01 (s, 2H, CH_2), 6.39 (s, 1H, ArH), 7.49 (d, 2H, J = 8.80 Hz, ArH), 7.87 (d, 2H, J = 8.80 Hz, ArH); Anal. Calcd for $C_{11}H_9ClN_6$: C, 50.68; H, 3.48; Cl, 13.60; N, 32.24. Found: C, 50.69; H, 3.52; N, 32.21. Compound **(d)**: yield: 33%; mp: 235–238 °C; MS (FAB): 306 (M^++1); IR (neat): ν = 3138, 1589, 1487, 1358, 1264 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.33 (s, 2H, CH_2), 6.59 (s, 1H, ArH), 7.62–7.71 (m, 4H, ArH); Anal. Calcd for $C_{11}H_9BrN_6$: C, 43.30; H, 2.97; N, 27.54. Found: C, 43.43; H, 2.93; N, 27.51. Compound **(e)**: yield: 55%; mp: >250 °C; MS (FAB): 233 (M^++1); IR (neat): ν = 3138, 1589, 1487, 1358, 1264 cm^{-1}; ^{1}H NMR (DMSO, 200 MHz) δ 3.9 (s, 2H, CH_2), 6.13 (s, 1H, ArH), 6.88–6.91 (m, 1H, ArH); 7.14–7.15 (m, 1H, ArH), 7.23–7.26 (m, 1H, ArH), 12.6 (s, 1H, ArH); Anal. Calcd for $C_9H_8N_6S$: C, 46.55; H, 3.45; N, 36.20. Found: C, 46.48; H, 3.67; N, 36.45. Compound **(f)**: yield: 43%; mp: >250 °C; MS (FAB): 267 (M^++1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.38 (s, 2H, CH_2), 6.62 (s, 1H, ArH), 7.19–7.35 (m, 3H, ArH), 7.58–7.68 (m, 2H, ArH); Anal. Calcd for $C_{13}H_{10}N_6O$: C, 58.64; H, 3.79; N, 31.56. Found: C, 58.66; H, 3.82; N, 31.49. Compound **(g)**: yield: 47%; mp: 204–205 °C; MS (FAB): 317 (M^++1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.15 (s, 3H, SCH_3), 2.81–2.88 (t, 2H, J = 6.56 Hz, CH_2), 4.14–4.20 (t, 2H, J = 6.52 Hz, CH_2), 4.28 (s, 2H, CH_2), 6.45 (s, 1H, ArH), 7.0 (d, 2H, J = 8.7 Hz, ArH), 7.64 (d, 2H, J = 8.7 Hz, ArH); Anal. Calcd for $C_{14}H_{16}N_6OS$: C, 53.15; H, 5.10; N, 26.56. Found: C, 53.20; H, 5.16; N, 26.54. Compound **(h)**: yield: 43%; mp >250 °C; MS (FAB): 390 (M^++1); IR (neat): ν = 3404, 2367, 1596, 1355, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.23 (s, 3H, NCH_3), 2.81–2.88 (t, 2H, J = 6.56 Hz, CH_2), 3.57 (s, 2H, CH_2), 3.99 (s, 2H, CH_2), 4.14–4.20 (t, 2H, J = 6.52 Hz, CH_2), 6.45 (s, 1H, ArH), 6.97–7.01 (d, 2H, J = 8.64 Hz, ArH), 7.06–7.15 (m, 5H, ArH), 7.62–7.66 (d, 2H, J = 8.70 Hz, ArH); Anal. Calcd for $C_{21}H_{23}N_7O$: C, 64.76; H, 5.95; N, 25.18. Found: C, 64.72; H, 5.87; N, 25.19.

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