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SYNTHESIS OF DIFFERENTLY SUBTITUTED 5-[4-(SULPHONYL) BENZYL] AND 5-[4-(ETHOXY) BENZYL]-2, 4-THIAZOLIDONEDIONE

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ABSTRACT

In an effort to develope better and safer antihyperglycemic thiazolidinediones than the available ones, some new substituted 5-[4-(Sulphonyl) benzyl] and 5-[4-(Ethoxy) benzyl]-2, 4-thiazolidonedione were synthesized. Structure Activity Relationship of some synthesized 2, 4-Thiazolidinediones closed to the marketed drugs of Antidiabetic e.g. Pioglitazone and Rosiglitazone.

Introduction

Diabetes mellitus is a complex metabolic disorder mainly characterized by hyperglycemia (high blood sugar) and other signs, as distinct from a single illness or condition. Treatment for type 2 diabetes, also called as non- insulin diabetes mellitus (NIDDM) is currently performed with a combination of exercise, restriction of calorie intake and drug therapy.

Oral hypoglycemic agents have been preferred by the clinicians in the control of blood sugar level of diabetes patients because of their effectiveness, better patient compliance over injectable insulin preparation and economy of treatment. A major problem with the use of sulphonylureas and injectable insulin preparations is occasional hypoglycemic shock which may be even fetal. In the recent years, the treatment of type 2 diabetes has been revotionazied with the advent of glitazones or thiazolidinediones (TZD's).[1]

A large number of antihyperglycemics 5-(substituted) benzyl-2, 4-thiazolidinediones have been reported during the last twenty years or so after the initial report of the activity of the ciglitazone, the prototype of this class of the drug. Ciglitazone (1) is not clinically used because of the toxicity associated with it but led to the development of more potent and clinically useful glitazones such as troglitazone (4), eglitazone (2) and rosiglitazone (3). Troglitazone was first marketed in the US in 1997 under the trade name ReZulin but had been banned and withdrawn from the US market due to hepatotoxicity in February 2000.[2]

In 1990, novel 5-(Naphtylalenyl sulphonyl)-2,4-thiazolidinedione (6)were reported to have antihyperglycemic activity in insulin – resistant animal models without the incidence of hypoglycemic episodes. More recently 5-(3-Aryl-2-propynyl)-5(arylsulphonyl) thiazolidine-2, 4-diones4 (5) have been reported to be antihyperglycemic agents.[3]

In the early 1940, the compounds 2-(p-aminobenzenesulphonamido)-5-isopropyl thiadiazole (IPTD)[6] (9) was used to treat typhoid fever and was withdrawn due to death of patients caused by it later, it was shown that the death caused by it was due to acute and prolonged hypoglycemia caused by stimulation of pancreatic insulin release.

In the present work, a systemic approach has been tried to introduce some of the structural features of IPTD in 5-(substituted benzyl)-2, 4-thiazolidinediones (14 and 23) to give some typical TZD's. In these compounds, 5-benzyl-2,4-thiazolidinedione moiety is predominately lipophilic having weakly acidic imino hydrogen in TZD moiety and is attached to the sulphonyl moiety of sulphonamido group and further, the sulphonamido nitrogen is attached to the heterocyclic lipophilic moieties which can alter the weakly acidic character of the sulphonamido hydrogen to different extents. Initially, only a very limited number of heterocyclic systems were introduced so as to verify wheather the final thiazolidinediones posses significant activity. In the series of the compounds (23), the structurally features of rosiglitazone, was largely maintained and only the N-methyl-2-pyridinyl amino moiety

was replaced by other amino substituted heterocyclic moieties. In the both series of compounds, the aim was to incorporate differently lipophilic moiety at the tail end of the resulting TZD's as well as to alter the extent of weak acidic character of the sulphonamido hydrogen in order to influence both pharmacokinetics and binding to the receptor sites in a favourable manner such that these factors may help to develop better and safer drugs than the available ones, and also to verify the usefulness of such moieties in maintaining the antihyperglycemic activity.

Chemistry-

Compounds were synthesized according to the methods summarized in schemes (1) and (2) respectively.

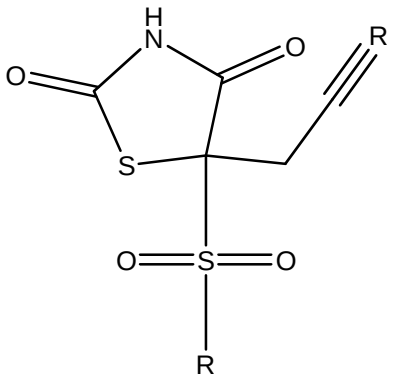
Appropriately substituted anilines (13) and (20) were diazotized and diazonium salt formed was treated with methyl acrylate at room temperature to obtain corresponding bromoester (14) and (21) in good yield (method D i.e.Meerwin arylation of anilines).

The corresponding bromoester were then reacted with thiourea and sodium acetate to get 5-subtituted 2-imino-thiazolidine-4-ones (15) and (22) in good yield (60- 80%) (Method E) which on oxidation with 2N HCl gives the corresponding thiazolidinediones (16) and (23) respectively, the target compounds (method F).[7]

Appropriately substituted anilines (20) which were used in the above reations were obtained by appropriate ethanolic alkaline (4N aqueous KOH 50 % +ethanol 50%) hydrolysis (method I) of the precursors 4-substiturted acetanilinide (19) and the yield of this step was always round or below 50% of the theory probably due to slow progress of their action under the reaction conditions (using heating and reflux for 24 hrs) and less stability of acetanilide derivatives (19) in the solvent mixture.

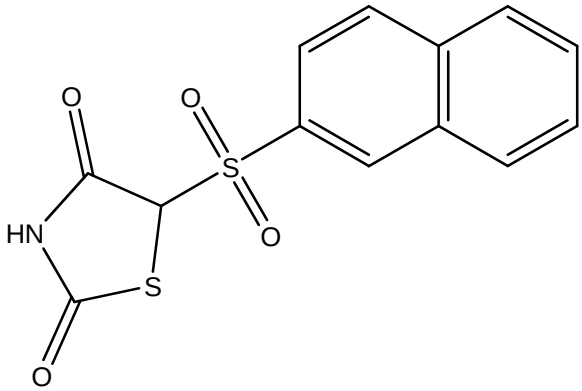
Acidic hydrolysis (method C) of substituted anilides (19) were tried but under these conditions the ether linkage attached to the para position was breaking and giving simply para hydroxyl aniline (para amino phenol) which was not desire at all because para amino phenol much prone to oxidation and polymerization which may further complicate the desired reaction and adversely affect the desired product.

However, acidic hydrolysis (method C)was preferred in case of substituted sulphonyl acetanilide (12) because hydrolysis was very fast (the required was just 20 minutes) and the yield of the reaction was also very good.i.e. 70-75 % compared to 50% yield of basic hydrolysis (method I).Also, acidic hydrolysis do not adversely affect the other moieties of the molecules unlike substituted ethoxy acetanilides (19) in which ether linkage can breakdown due to hydrolysis.



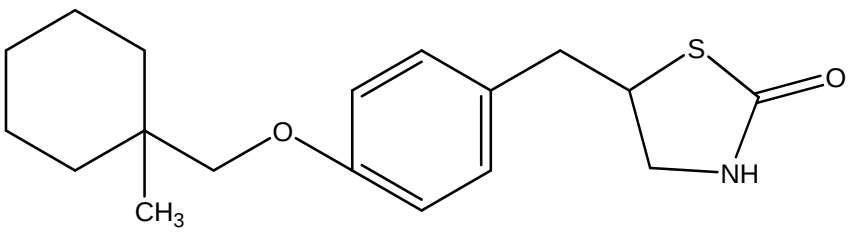
R=aryl

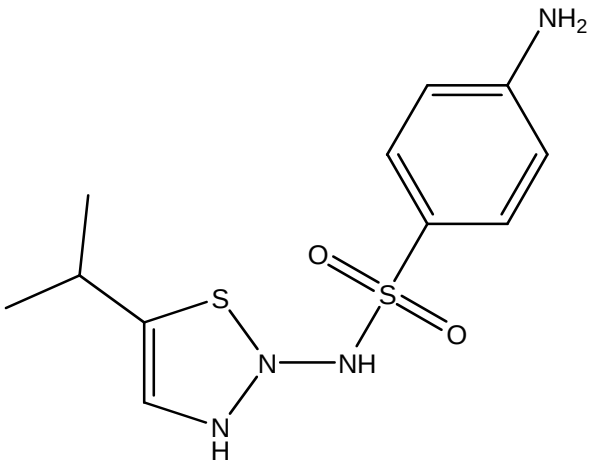
5-(3-aryl-2-propynyl)-5-arylsulphonyl)thiazolidine 2,4-dione



5-(Napthylenyl sulphonyl)-thiazolidine-2,4-dione

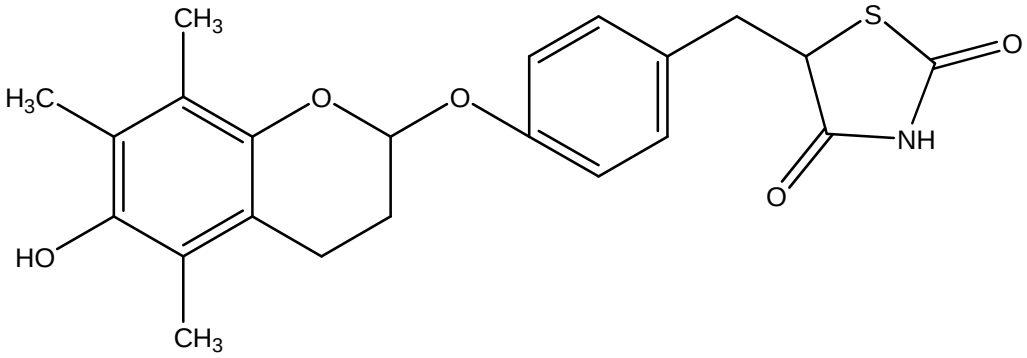
Ciglitazone



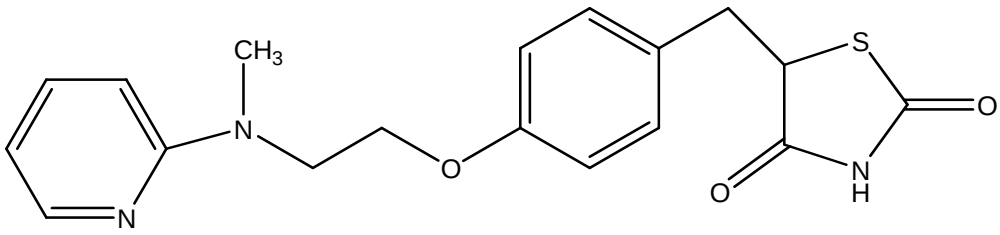


2-(p-aminobenzenesulphonamido)-5-isopropyl thidiazole

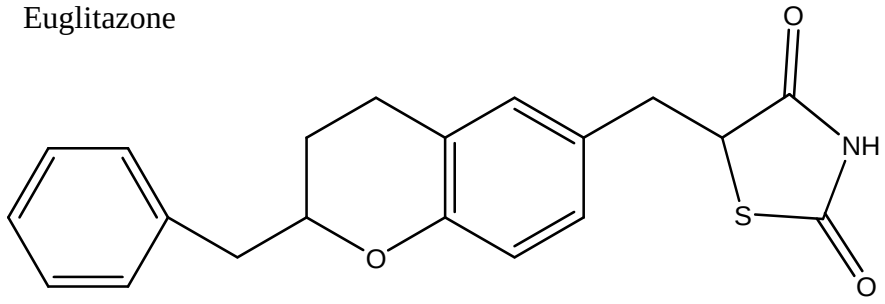
Troglitazone

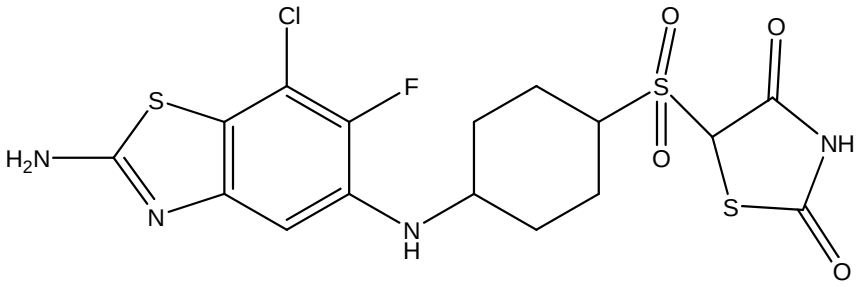


Rosiglitazone

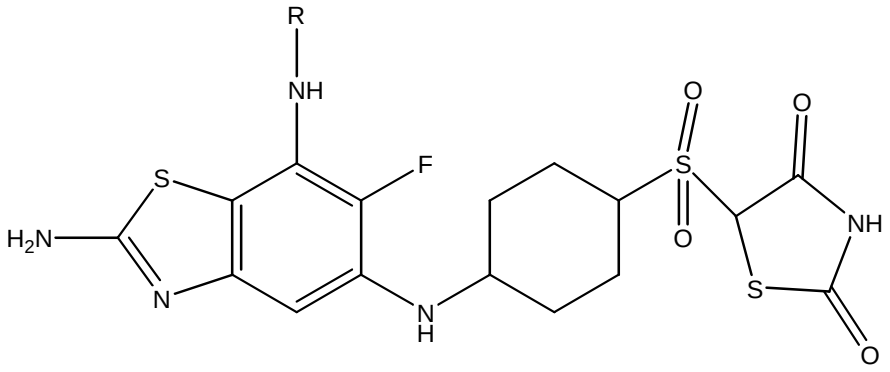


Euglitazone



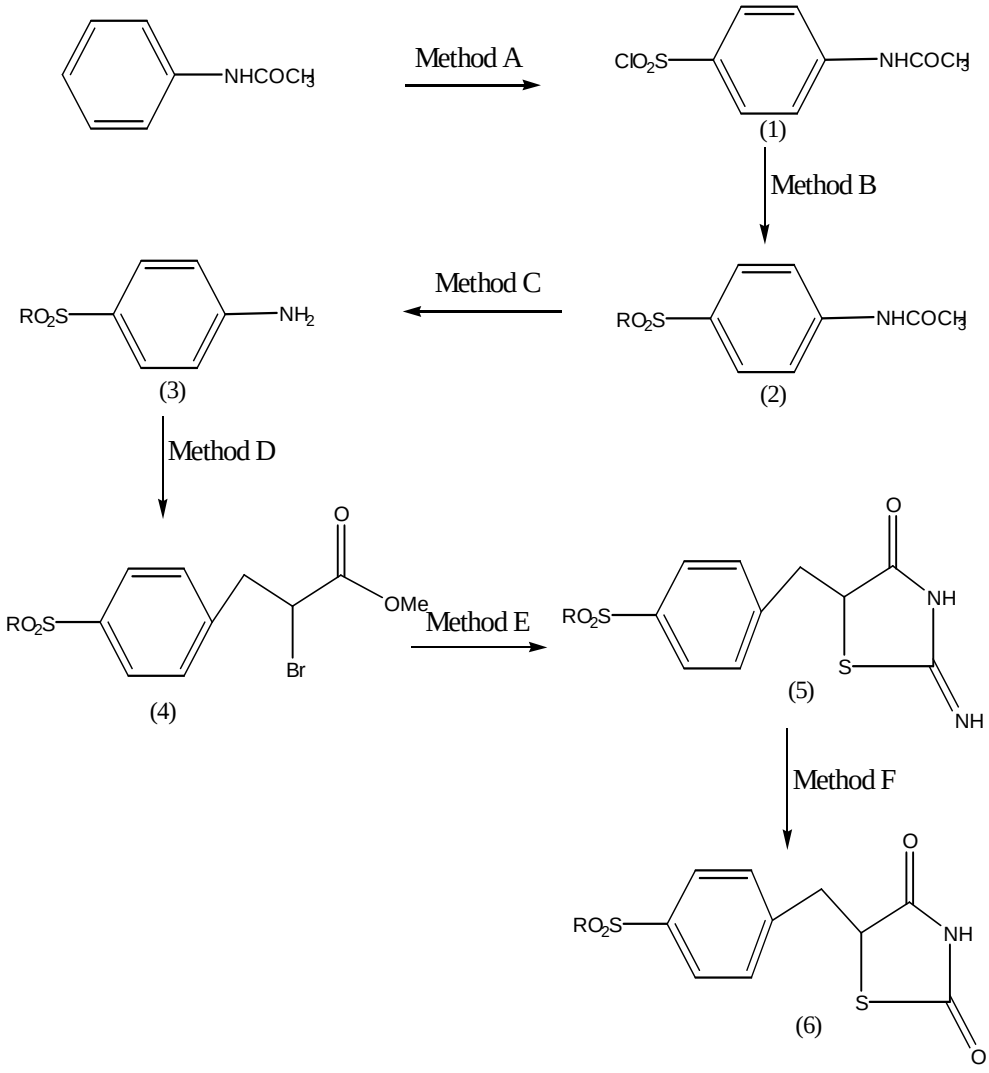


2-Amino-[5-(4-sulphonylbenzylidene)-2,4-thiazolidinedione]-7-chloro-6-floro benzothiazole

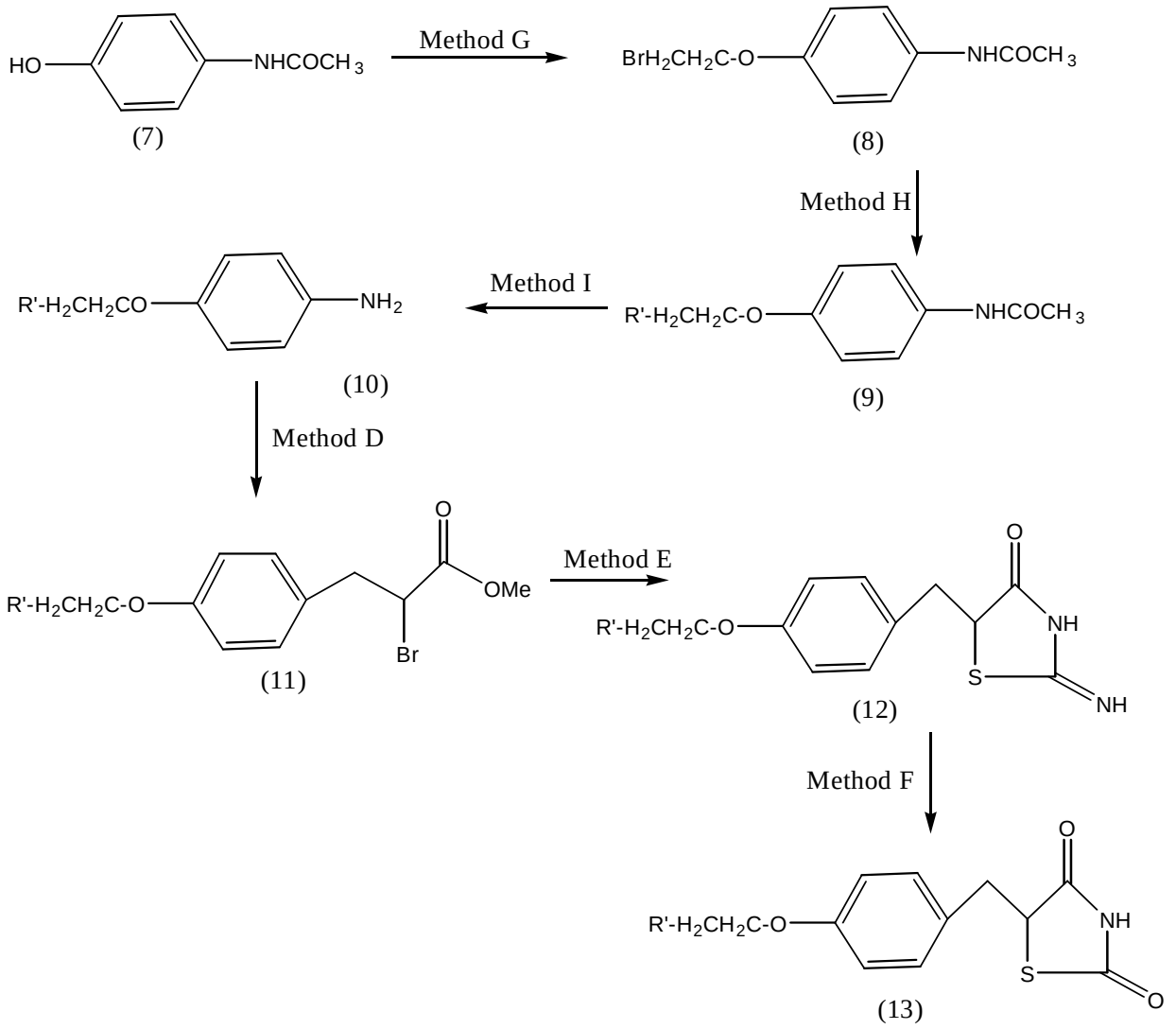


2-Amino-[5-(4-sulphonylbenzylidene)-2,4-thiazolidinedione]-7-(substituted amino)-6-floro benzothiazole

Synthesis of substituted 5-[4-(sulphonyl)benzyl]-2,4-thiazolidinediones.



Method A: acetanilide, chlorosulphonic acid; Method B: dry pyridine, acetone, R [substituted amines]; Method C: concentrated HCl, ethanol; Method D: NaNO2, HBr, Cuprous oxide, methyl acrylate at 0-5ºc; Method E: Thiourea, sodium acetate; Method F: 2N HCl, ethanol.



Method G: Paracetamol, ethylene dibromide, sodium-ethoxide; Method H: dry pyridine, potassium hydroxide, R [substituted amine]; Method I: concentrated HCl, ethanol; Method D: $NaNO_2$, HBr, Cuprous oxide, methyl acrylate at 0-5ºc; Method E: Thiourea, sodium acetate; Method F: 2N HCl, ethanol.

Results and Discussion

The structures of the synthesized substituted thiazolidinediones were elucidated by elementary analysis, 1n NMR, Mass and IR findings. All data were in accordance with the assumed structures.IR spectra of the compounds showed C^4=O and C^2=O stretching bands of 2,4-TZD at 1729-1740 cm-1 and 1666-1686cm^{-1}, respectively.

As it is documented in various literature that the 5-(p-substituted benzyl) 2, 4-thiazolidinediones moiety is essential for activity of the compounds of this class in all the synthesized compounds variation is made only at para position of benzyl moiety. In the compounds (16), the para substitution is (aromatic or substituted aromatic or heteroaromatic) aminosulphonyl moiety and all these compounds were synthesized very successfully. It was done to verify which of those substituents offer better structural makeup for binding of the compounds with the receptors and producing activity. In other compounds i.e. compounds (21), heteroarmatic ethoxy moiety was kept to maintain similarity with the clinically useful drugs e.g. rosiglitazone with variation only in the heterocyclic moiety. It was done to verify the effect of other nitrogen containing heterocyclic on activity in place of pyridine ring of rosigltazone.

Scheme 1: Substituted 5-[4-(Sulphonyl) benzyl] 2, 4-thiazolidonedione

Compound	R	Synthetic Method	Formula	M.P.	% yield	I.R. Peaks
A1	2-Amino-6-methyl-benzothiazole	A,B,C,D, E,F	$C_{18}H_{15}N_3O_4S_3$	171-175	55.55	1334,3106,1523,1647, 1701,608,3059
A2	2-Amino-6-chloro-benzothiazole	A,B,C,D, E,F	$C_{17}H_{12}N3O_4S_3Cl$	177-180	44.11	1325,3273,3091,1701, 1753,1631,565,651
A3	2-Amino-6-bromo-benzothiazole	A,B,C,D, E,F	$C_{17}H_{12}N_3O_4S_3Br$	182-184	54.50	1315,3273,3086,1622, 1699,1518,563,705
A4	2-Amino-6-methoxy-benzothiazole	A,B,C,D, E,F	$C_{18}H_{15}N_3O_5S_3$	175-178	44.98	1305,3383,3088,1637, 1697,1602,569,692

A5	2-Amino-benzothiazole	A,B,C,D, E,F	$C_{17}H_{13}N_3O_4S_3$	162-163	64.25	1321,3282,3061,1616, 1768,569,634
A6	Diphenyl-amino	A,B,C,D, E,F	$C_{22}H_{18}N_2O_4S_2$	155-156	50.37	1342,3384,1750,569,3042,1590
A7	Napthyl-amino	A,B,C,D, E,F	$C_{20}H_{16}N_2O_4S_2$	165-166	51.26	1292,3232,1085,1749, 1629,570,3049,1583
A8	3-Chloro-4-flouroaniline	A,B,C,D, E,F	$C_{16}H_{14}N_2O_4S_2$	148-150	49.82	1383,3213,3059,1695, 1776,572,694,759
A9	2-Hydroxy aniline	A,B,C,D, E,F	$C_{16}H_{14}N_2O_4S_2$	179-180	50.55	3394,3481,3650,626,3010,1457,1708,1770,1255,1005,1257
A10	2-nitroaniline	A,B,C,D, E,F	$C_{16}H_{13}N_3O_6S_2$	219-220	58.00	3449,3375,1546,659,3018,,1546,1672,1760, 2883.
A11	3-chloroaniline	A,B,C,D, E,F	$C_{16}H_{13}N_2O_4S_2ClF$	182-184	61.55	3369,3475,626,654,2967,1593,1693,1782
A12	2,5-dichloroaniline	A,B,C,D, E,F	$C_{16}H_{15}N_2O_4S_2Cl_2$	191-193	57.52	3278,3481,756,630,2901,1583,1699,1740,3078
A13	4-hydroxy aniline	A,B,C,D, E,F	$C_{16}H_{14}N_2O_5S_2$	158-160	52.55	3382,3493,1408,622,2955,1464,1700,1770,3028
A14	4-nitroaniline	A,B,C,D, E,F	$C_{16}H_{13}N_3O_6O_2$	172-173	55.64	3302,3373,1406,641,3009,1582,1599,1700,2847,1141.
A15	2,6-dichloroaniline	A,B,C,D, E,F	$C_{16}H_{15}N_2O_4S_2Cl_2$	204-207	55.55	3392,3481,786,735,580,2924,1483,691,1734,2854
A16	N-benzimidazole	A,B,C,D, E,F	$C_{17}H_{13}N_4O_3S_2$	162-165	55.55	2957,3333,650,2820,1503,1615,1350,1687,1746.

Scheme2: Substituted 5-[4-(ethoxy) benzyl] 2, 4-thiazolidonedione

Compound	R	Synthetic Method	Formula	M.P.	% yield	I.R. Peaks
A17	N-benzimidazole	G,H,I,D, E,F	$C_{18}H_{16}N4O_3S$	235-236	55.23	3049,1739,1685,1606, 676,1060,1160,651,1236
A18	3-formyl indole	G,H,I,D, E,F	$C_{21}H_{18}N_2O_4S$	210-211	54.00	3437,1624,1506,1006, 831,1234
A19	2-aminopyridine	G,H,I,D, E,F	$C_{17}H_{17}N_3O_3S$	220-211	66.00	3246,1622,1404,658,1184
A20	N-piperizine	G,H,I,D, E,F	$C_{13}H_{27}N_3O_3S$	199-200	83.00	3205,1622,1404,658,1184
A21	2,4,5-triphenylimidazole	G,H,I,D, E,F	$C_{18}H_{27}N_3O_3S$	210-213	46.00	3051,1744,1689,1595, 607,1315,1236,1485
A22	1-phenylnapthalmine	G,H,I,D, E,F	$C_{19}H_{17}N_3O_3S_2$	190-192	66.00	1440,3464,2929,1680, 1429,1581,1016
A23	2-aminobenzthiazole	G,H,I,D, E,F	$C_{19}H_{17}N_3O_3S_2$	287-288	62.00	1016,3053,1730,1690, 1605,590,680,1238,1042.

Experimental

Preparation of p-(acetamidobenzene) sulphonyl chloride (11)

Frequently shaked a solution of dry acetanilide (20gm, 0.148 mol) and chlorosulphonic acid (50ml, 90gm,0.77 mol) was heated at 1000C for 1 hour, cooled, poured into ice – water. The reaction mixture was filtered to afford the title compound as a granular white solid.

Preparation of p-(Substituted) sulphonyl acetanilide (12)

Substituted amine (0.05 mol) was dissolved in mixture of anhydrous acetone (40 ml) and dry pyridine (6 ml) and added 0.05 mol) pure p-acetamidobenzene sulphonyl chloride. The reaction mixture was set aside overnight and filtered the product.

Preparation of p-(substituted sulphonyl) aniline (13)

The substituted sulphonyl acetanilide was hydrolyzed by ethanol (75 ml) and concentrated hydrochloric acid (15 ml) for 20 minutes. The cooled solution was diluted with concentrated ammonia solution to afford to afford the title compound.

Preparation of Methyl-2-bromo-3-(4-(para substituted) phenyl) Propionate (14 or 21)

A solution of sodium nitrite (NaNO2) (4.2 gm, 0.06 mol) in water (7.5 ml) was added dropwise to a stirred and ice cold mixture of appropriate p-substituted aniline.(0.055 mol), aqueous hydrobromic acid (47%, 37.6gm, 0.22mol), methanol (50 ml) and acetone (125 ml) below 50c. The whole reaction mixture was stirred at 50c for 30 minutes and then, Methyl acrylate (30 ml, 0.33mol) was added and the temperature was slowly raised to 380c. Powdered cuprous oxide (0.5 gm) was added. After nitrogen evolution has ceased, the reaction mixture was concentrated in vacuo. The residue was diluted with water, made alkaline with concentrated ammonia and extracted with ethyl acetate and dried over anhydrous magnesium sulphate and concentrated in vacuo to afford the title compound.

Preparation of 2-imino-5-(4-(substituted) benzyl)-4-thiazolidinone (15 or 22)

A mixture of methyl [2-bromo-3-{4-(para-substituted) phenyl} propionate, a crude oil (21mmol), (14 or21), thiourea (2.1gm, 21 mmol) ,ethanol (80ml) & sodium acetate (2.3 gm,0.328 mol) was stirred under reflux for 3 hour and concentrated in vacuo. The residue was neutralized with aqueous sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate extract was concentrated in vacuo to afford the title compound.

Preparation of 5-{4-(substituted) benzyl}-thiazolidine-2,4-diones(16 or 23)

A mixture of 2-imino-5-[4-(substituted) benzyl}-4-thiazolidinone (10 mmol), 2N hydrochloric acid (50ml) was stirred under reflux for 12 hour. The reaction mixture was concentrated in vacuo. The residue was diluted with water, neutralized with saturated aqueous sodium bicarbonate, extracted with chloroform and dried over anhydrous. Magnesium sulphate, and then concentrated in vacuo to afford the title compound.

Preparation of 4-[2-(Bromoethoxy) acetanilide] (18)

To 533 ml of dry ethanol, 20.4 gm (0.88 mol) of sodium metal was added slowly in small pieces, cooled then paracetamol (120 gm, 0.88 mol)(20) was added followed by slow addition of ethylene dibromide (76.16ml, 153gm, 0.88mol). The reaction mixture was poured into ice cold water and precipitated solid was collected by filtration under suction.

Preparation of 4-[2-(Heterocyclyl /heterocyclylamino) ethoxy] acetanilide (19)

To solution of an appropriate heterocyclic compounds or amino substituted heterocyclic hydroxide base and the reaction dry dimethylformamide (DMF) (37.5 ml) at 25oC was added potassium hydroxide base and the reaction mixture was stirred for 0.25 01 hr. A solution of 4-[2-{bromoehoxy}]acetanilide (18) in dry DMF (12.5)was added and stirred further for 1-6 hr.The reaction mixture was poured into ice water and precipitated solid was filtered under suction.

Preparation of [2-(Heterocyclyl /heterocyclylamino) ethoxy] aniline (20)

A mixture of 4-[2-(Heterocyclyl /heterocyclylamino) ethoxy] acetanilide (19)(16 mol), $N potassium hydroxide (75 ml) was refluxed for 24 hr and poured into ice cold water and the precipitated solid was filtered under suction.

Conclusion

In conclusion, we have found a new reaction that was carried out between acetanilide with chlorosulphonic acid and paracetamol with ethylene bromide to give N-substituted thiazolidinediones through the intramolecular nucleophilic substitution reaction.

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