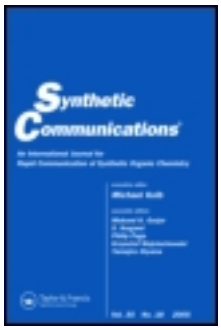


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

An Efficient and Convenient Synthesis of 1, 4-benzoxazines, 1, 4-benzothiazines, Spiro-1, 4-benzoxazines, and Spiro-1, 4-benzothiazines

Samundeeswari L. Shastri [a], Bahubali M. Chougala [a], Manohar V. Kulkarni [a] & Lokesh A. Shastri [a]

[a] Department of Chemistry, Karnatak University, Dharwad, India

Accepted author version posted online: 26 Mar 2013.

To cite this article: Samundeeswari L. Shastri , Bahubali M. Chougala , Manohar V. Kulkarni & Lokesh A. Shastri (2013): An Efficient and Convenient Synthesis of 1, 4-benzoxazines, 1, 4-benzothiazines, Spiro-1, 4-benzoxazines, and Spiro-1, 4-benzothiazines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI:10.1080/00397911.2012.714829

To link to this article: http://dx.doi.org/10.1080/00397911.2012.714829

AN EFFICIENT AND CONVENIENT SYNTHESIS OF 1, 4-BENZOXAZINES, 1, 4-BENZOTHIAZINES, SPIRO-1, 4-BENZOXAZINES, AND SPIRO-1, 4-BENZOTHIAZINES

Samundeeswari L. Shastri[1], Bahubali M. Chougala[1], Manohar V. Kulkarni[1], Lokesh A. Shastri[1]

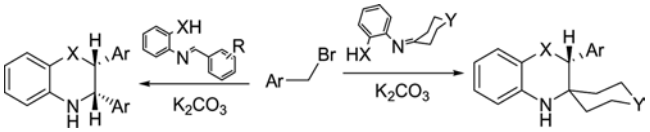
[1]Department of Chemistry, Karnatak University, Dharwad, India

Corresponding author. Tel.: +91 836 2215286; fax: +91 836 2747884; E-mail: chemilok@yahoo.co.in

Abstract

An efficient, convenient, synthesis of 1, 4-benzoxazines, 1,4-benzothiazines, spiro-1, 4-benzoxazines and spiro-1, 4-benzothiazines derivatives were accomplished in good yields via the novel intramolecular cyclisation mediated by mild base K_2CO_3 in ethanol solvent. A variety of substrates can participate in the process with good yields, making this methodology have broad applicability. All the structures of synthesised compound have been confirmed by spectral analysis.

Supplemental materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® to view the free supplemental file.



KEYWORDS: 4-bromomethylcoumarin, Schiff base, 1, 4-benzoxazines, 1,4-benzothiazines, spiro-1, 4-benzoxazines, spiro-1, 4-benzothiazines and intramolecular.

1. INTRODUCTION

Recently,organic chemistry receives increasing attention because they address diversity,in development of pharmaceutical industries and is main interest to discover the new drug entities.Therefore, the organic chemists have developeda new synthetic methods and technologies,according to the need of industries,to obtain expected compounds in a pure and efficient. Hence, among these the multicomponent reactions(MCRs)are offer the favourable condition for constructing a complex molecules with exceptional synthetic efficiency and high stereo selectivity, from easily available starting materials.[1–4]Therefore, MCRs is now well established technique organic chemistry for the synthesis of vastnumber of compounds at short time[5–7]and also straightforward approach.[8]The intrinsic cytotoxicity study was done from a series of newly synthesised 8-amino (Figure **1**) and 2-amino-1,4-benzoxazine (Figure **1a**) derivatives, which areable to inhibit oxidative stress-mediated neuronal degeneration in neuronal cell cultures. Thus, the 1,4-benzoxazines were showing more potent neuroprotective activity, without affecting the intrinsic cytotoxicity.[9,10]The structural activity relationship studies of 1,4-benzoxazines (Figure **2**) and combined results of both intrinsic cytotoxicity and neuro protection results confirms 1,4-benzoxazines derivatives are more potential and effective in protecting against the lesions induced by *S*-bromo-willardiine injected into the cortex of 5-day old mice-pups,[11] and exhibited diverse biological activity.[12–16]

A verity of electrochemical multistep one-pot synthesis of 2-alkylamino-1,4-benzoxazine and 2-hydroxy -1,4-benzoxazine (Figure **3**) derivatives werereported[17,18]via inverse-

electron-demand Diels-Alder reaction of an *o*-iminoquinone diene and a secondary alkylenamine dienophile. 2-Aminophenols and 2-nitrophenols have been widely used as the starting materials for thesynthesis of 1,4-benzoxazines. In the case of 2-nitrophenols, the initial O-alkylation was followed by nitro reduction and subsequent intramolecular *N*-substitution,[19]and with 2-haloalkanoyl chlorides or bromide in the first place to form the 2-aminophenols, which then underwent an intramolecular O- alkylation on heating in the presence of base.[20–22]

Similarly several substituted 1,4-benzothiazine derivatives are currently of interest due to their therapeutic role as smooth muscle relaxants [23] potassium channel-opening agents,[24]urokinase inhibitors[25] and calcium antagonists.[26–28]Therefore, thenew chiral benzothiazines(Figure **5**)wereascribed and this classof benzothiazines derivatives, opens the way to development of newinhibitors for carbohydrate processing enzymes of therapeutic importance.[29]The synthetic chemotherapeuticantibioticlevofloxacin drug has been reported by short route synthesis through palladium mediated amination to 1,4-benzoxazines and 1,4-benzothiazines[30] via *tele* nucleophilic aromatic substitution.[31]

Thebiosynthesis of pheomelanins is the typical epidermal pigment of red haired, Celtic-type Caucasians, arise from oxidative cyclisation of cysteinyldopas, mainly the 5-*S*-isomer, via 1,4-benzothiazines (Figure **6**).[32–34] The structural modification of 1,4-benzothiazines, attracts the greater pharmacological activity and some of the methods used for the synthesis of these compounds on condensation of 2-aminothiophenols, with α,β- unsaturated acids or halo acetic acid /esters. Hence only few synthesis of

intramolecular hetero cyclisation of S-methylene derivatives of spiro-fused benzothiazines has been prepared (Figure 7**)**.[35–37]

In view of these observations and our ongoing interest in the chemistry of 1,4-benzothiazines[38] and 1,4-benzoxazines, the complexity of the existing methods, it is sure that a simpler method isnecessary for the synthesis of aryl substituted title compounds.

2. RESULTS AND DISCUSSION

We have considered worthwhile to explore the reactions depicted in the following schemes 1 to 6 and considered the possibility of synthesizing desired compounds in a single synthetic operation from arylalkylhalides and aldehydes/cyclic ketoneswith 2-aminophenol/2-aminothiophenol. Thus, we hypothesized that, an intramolecular carbanion addition across the imine carbon, by an appropriate reagent, in a three component systemthrough simple approach. Taking into consideration all the above-mentioned points we thought that the combination of all the three substrates under mild experimental condition by single synthetic approach using L-proline as catalyst. The L-proline favours the desired product**10** with very pooryield**.**

Hence, we initiated our studies with the reactions of 4-bromomethylcoumarins (**7**), 2-aminophenol/2-aminothiophenol **(8)**with aromatic aldehydes (**9)**and L-proline in presence of dichlomethane (DCM) as a solvent, at room temperature for 18 hrs under stirring (Scheme 1), these reactions led to the formation of the 1,4-benzoxazines(**10** = **O**)/ 1,4-benzothiazine (**10 = S**)at low yield (10-15%) along with other isolated intermediate

productsare (**10 (i)** 50% and **10 (ii)**30%). The same reaction at refluxing temperature we observed **10(i)**is the major product (70 %). Therefore, our initial efforts were directed to finding the appropriate reagent and reaction conditions to perform the proposed sequence in Scheme 2 starting from 4-bromomethylcoumarins (**7**)[35] with Schiff base (**11**) which is derived from 2-aminophenol and substituted aldehydes. Regarding the reagent for the intramolecular carbanion addition across the imine carbon for two component systems(Scheme 2), we considered anhydrous potassium carbonate asmild base, of their ability to activate the functionalityof hydroxyl group under mild condition at room temperature followed by *in situ* formation of carbanion, on methylene carbon and add to imine carbon to lead compound **10.**Thus, this approach led as single product **10** without any other side products and the obtained product showed a characteristic NH stretching band in IR around 3300-3400 cm^{-1} and ^1H NMR showed two doublet around 4.56and 5.59δppm (J= 6.6 Hz)is due to C_2-H and C_3-H respectively. The NH is D_2O exchanges around 6.71δppm andthe results of physical analysis data are summarised in Table 1.

The scope of the reaction was surveyed by probing changes to the benzyl bromide (**12**), and the Schiff base (**13**) substrates. The flexibility of the method allows the desired product (**14**&**15**) in low yield (Scheme 3). The isolated compounds showed characteristic IR NH stretching band and two doublets around 4.41 and 5.07 δppm (J=7.0 Hz) in ^1H NMR.The yield drop wasobserved, which is compared with coumarin system, it may be due to the generation of carbanion is difficult and less favourable in this system by anhydrous potassium carbonate condition. In the case of coumarin system, formation of

carbanion is more feasible due to the stabilisation via enolate form (Scheme 2) and the results are summarised in Table 2.

Many of the synthetic spiro-benzothiazines derivatives display important structural features, but very limited number of synthetic methods for this kind of compounds was reported. However, these methods suffer from tedious synthetic routes, long reaction timeand drastic reaction conditions. The developments of new protocols for the synthesis of complex spiro-cyclic compounds are still remains a great challenge to synthetic chemists due to their associated reactivity patterns. In particular, the spiro-1,4-benzothiazines and spiro-1,4-benzoxazines framework. On the basis of our progressive endeavors in exploring new methodologies toward spiro-1,4-benzothiazines, and spiro-1,4-benzoxazines, we report herein, a two component reaction involving **7** and **16** inethanol to provide spiro- 1,4-benzoxazines (**17**) /1,4-benzothiazines (**18**)found by serendipity with good yield (Scheme4). The results are summarised in Table 3. In other hand the reaction between benzyl bromide (**12**) and imine (**16**),the isolated products (**19**) and (**20**) shows less yield (Scheme 5)compared with(**17)** and (**18)** (scheme 4).The isolated products showed characteristic NH stretching band in IR around 3318 cm^{-1} and singlet around 4.24 δppm in ^{1}H NMR. All synthesised compounds structure has been confirmed by IR, ^{1}H NMR,^{13}C NMR and mass spectra (see supplementary file). The results are summarised in Table 4.

3. CONCLUTION

In summary, we have demonstrated a simple and facile two component reaction for the synthesis of 1,4-benzoxazines, 1,4-benzothiazine, spiro-1,4-benzoxazines and spiro-1,4-benzothiazine derivativesfrom4-bromomethylcoumarins and benzyl bromiderespectively, by using potassium carbonate which played the role of base. The simplicity of approach makes this strategy useful for the synthesis of spiro-frameworks. Further studies to delineate the scope and limitations of the present methodology are underway.

4. EXPERIMENTAL

General Procedures

Melting points were recorded from sheetal scientific instrument and presented in degree centigrade. IR spectra were recorded on a Nicolet-impact – 410 FT infrared spectrometer. The NMR was recorded on a Bruker 300 and 400 MHz FT NMR spectrometer. ^{1}H and ^{13}C Chemical shift were represented as δppm values relative to the internal standard, trimethylsilane. 4-bromomethylcoumarin **1**[35] was prepared according to our earlier report and substituted aromatic aldehydes and cyclic ketones were used commercially.

Generalexperimental Procedure For Synthesis Of 10, 17 And 18

The substituted 4-bromomethyl coumarins (**7**) (1.0equiv.) was refluxed with Schiff base (**11/16**) (1.0 equiv.) and potassium carbonate (2.0 equiv.) in 20mL of dry ethanol on a water bath for 8-10 hrs. The reaction mixture was cooled and filtered to remove potassium carbonate. The filtrate was concentrated and added into crushed ice. The solid separated was filtered and the residue was washed with dilute hydrochloric acid (1N) 20 mL followed by water wash and recrystallized from ethanol solvent.

4-(3-(4-Chlropheny)-3,4-Dihydro-2*H*-Benzo[B][1,4]Oxazin-2-Yl)-6-Methoxy-2*H*-Chromon-2-One (10o)

Light brown solid, Yield 82%, mp: 153 ^{o}C. IR (KBr) ν 1705, 3315 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.71(s, 3H, OCH_3), 4.56(d, 1H, C-H, J = 6.6 Hz), 5.59 (d, 1H, C-H, J = 6.6 Hz), 6.53(s, 1H, C_3-H of coum), 6.60 (m, 1H, Ar-H), 6.88(s, 1H, NH and D_2O exchanges), 6.60-6.84(m, 3H, Ar-H), 7.00 (d, 1H, Ar-H, J= 2.69 Hz), 7.09 (dd 1H, Ar-H, J = 9.00 Hz), 7.25 (dd, 3H, Ar-H, J = 8.4 Hz), 7.39 (d, 2H, Ar-H, J = 8.4 Hz) ; ^{13}C NMR (400 MHz, DMSO-d_6): 52.56, 58.23, 67.30, 113,12, 116.16, 116.91, 117.11, 117.96, 119.04, 121.26, 123.63, 124.23, 125.51, 125.85, 129.82, 130.43, 134.78, 144.56, 145.31, 148.46, 152.51, 153.90, 161.88: Mol.F.$C_{24}H_{18}ClNO_4$ mass: 419.09; LC-MS found: m/z 419.8 (98.8%).

General Experimental Procedure For Synthesis Of 14, 15, 19 And 20

The benzyl bromide (**12**) (1.0equiv.) was refluxed with Schiff base (**13/16)** (1.0 equiv.) and potassium carbonate (2.0 equiv.) in 20 mL of dry ethanol on a water bath for 8-10 hrs. The reaction mixture was cooled and filtered to remove potassium carbonate. The filtrate was concentrated and added into crushed ice. The solid separated was filtered and the residue was washed with dilute hydrochloric acid (1N) 20 mL followed by water wash. The isolated compound was purified by column chromatography by using ethyl acetate : hexane (3:7).

3,4-Dihydro-2,3-Diphenyl-2H-Benzo[B][1,4]Oxazine (14a)

Light yellow solid, Yield 30%, mp: 128 ^{o}C. IR (KBr) ν 1619, 3360 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$): δ_H 4.41(d, 1H, C-H, J = 7.0 Hz), 5.07(d, 1H, C-H, J = 7.0 Hz), 6.64-7.09(m, 15H, Ar-H and NH and NH D_2O exchanges); ^{13}C NMR (400 MHz, DMSO-d_6): 56.42, 67.88, 123.52, 125.38, 125.65, 126.48, 127.02, 128.10, 128.58, 128.96, 129.09, 129.88, 132.02, 141.26, 141.86, 143.01: Mol.F.$C_{20}H_{17}NO$ mass: 287.13; GC-MS found: m/z 287.0 (95.7%)

ACKNOWLEDGEMENTS

We acknowledge the University Grant Commission, New Delhi (UGC) and Department of Science and Technology, New Delhi (DST) for the financial support.

REFERENCES

1. Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH, Weinheim, **2006**.

2. DJmling, A.; Ugi, I. Multicomponent Reactions with Isocyanides, *Angew. Chem.* **2000**, *112*, 3300 - 3344; *Angew. Chem. Int. Ed*. **2000**, *39*, 3168 -3210.

3. Tietze, L. F. Reactions in Organic Synthesis. *Chem. Rev.* **1996**, *96*, 115-136.

4. Tietze, L. F.; Beifuss, U. Sequentielle Transformationen in der Organischen Chemie eine Synthesestrategie mit Zukunft. *Angew. Chem.* **1993**, *105*, 137-170.

5. Ugi, I. IsonitrileChemistry; Academic Press: New York, 1971.

6.Ugi, I. Multicomponent Reactions in Total Synthesis. *J. Prakt. Chem.* **1997**, *339*, 499-516.

7. Umesh, R. P.; Dhanaji, V. J.; Balaji, S. L.; Ramrao, A. M.Baker's yeast catalyzed synthesis of 1,4-benzothiazines, performed under ultrasonication. *J. Molecul.Catal.B*. **2011**, *68*, 94-97.

8.Uli, K.; Andrea, P. A straightforward approach towards 5-substituted thiazolylpeptides *via* the thio-Ugi –reaction. *Org. Biomol. Chem.* **2010**, *8*, 5442-5447.

9. Martine, L.; Brian, L.; Bruno, P.; Fleury, M. B. Synthesis and in Vitro Evaluation of New 8-Amino-1,4-benzoxazine Derivatives as Neuroprotective Antioxidants, *J. Med. Chem.* **1999**, *42*, 5043-5052.

10. Estelle, B.; Brian, L.; Pierre, L.; Leslie, S.; Pierre, G.;Fleury, M. B.; Martine, L.Novel 2-Alkylamino-1,4-benzoxazine Derivatives as Potent Neuroprotective Agents: Structure−Activity Relationship Studies. *J. Med. Chem.* **2005**, *48*, 1282-1286.

11. Largeron, M.; Mesples, B.; Gressens, P.; Cechelli, R.; Spedding, M.; Le Ridant, A.; Fleury, M. B. *Eur. J. Pharmacol.* **2001**, *424*, 189-194.

12. Kuroita, T.; Marubayashi, N.; Sano, M.; Kanzoki, K.; Inoba, K.; Kawakita, T. *Chem. Pharm. Bull.* **1996**, *44*, 2051-2060.

13.Caliendo, G.; Griew, P.; Perssutti, E.; Santagada, V.; Santini, A.; Alberizio, S.; Fattorusso, C.; Pinto, A.; Sorrentino, R. Synthesis, biological activity and conformational study of 1,4-benzoxazine derivatives as potassium channel modulators. *Eur. J. Med. Chem.* **1998**, *33*, 957-967.

14. Caliendo, G.; Perssutti, E.; Santagada, V.; Fiorino, F.; Severino, B. d'Emmanuele diVilla Bionca, R.; Lippolis, L.; Pinto, A.; Sorrentino, R. Synthesis and vasorelaxant activity of new 1,4-benzoxazine derivatives potassium channel openers. *Bioorg. Med.Chem.* **2002**, *10*, 2663-2669.

ACCEPTED MANUSCRIPT

15. Sebille, S.; deTullio, P.; Boverie, S.; Antoine, M. H.; Lebrun, P.; Pirotte, B.Recent developments in the chemistry of potassium channel activators: the cromakalim analogs. *Curr. Med.Chem.* **2004**, *11*, 1213-1222.

16. Matsuoka, H.; Ohi, N.; Mihara,M.; Suzuki, H.; Miyamota, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Tekeda, Y.; Yano, K.; Kuroki, T.Antirheumatic Agents: Novel Methotrexate Derivatives Bearing a Benzoxazine or Benzothiazine Moiety. *J. Med. Chem*. **1997**, *40*, 105- 111.

17. Estelle, B.; Fleury, M. B.; Martine, L. Simultaneously Electrogenerated Cycloaddition Partners for Regiospecific Inverse-Electron-Demand Diels−Alder Reactions: A Route for Polyfunctionalized 1,4-Benzoxazine Derivatives. *J. Org. Chem.* **2004**, *69*, 882-890.

18. Daiwang, X.; Angele, C.; Fleury, M. B.; Martine, L. Electrochemically Induced Cascade Reaction for the Assembly of Libraries of Biologically Relevant 1,4-Benzoxazine Derivatives. *J. Org. Chem.* **2006**, *71*, 6374-6381.

19. Touzeau, F.; Arrault, A.; Guillaumet, G.; Scalbert, E.; Pfeiffer, B.; Rettori, M.; Renard, P.; Merour, J-Y. Synthesis and Biological Evaluation of New 2-(4,5-Dihydro-1*H*-imidazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine Derivatives. *J. Med. Chem.* **2003**, *46*, 1962-1979.

20. Arrault, A.; Touzeau, F.; Guillaumet, G.; Leger, J.-M.; Jarry, C.; Merour, J.-Y. Synthesis of functionalised pyrido[4,3-*b*][1,4]oxazine and imidazo[1,2-*a*]pyridine derivatives. *Tetrahedron* **2002**, *58*, 8145-8152.

ACCEPTED MANUSCRIPT

21. Lee, C. L.; Chan, K. P.; Lam, Y.; Lee, S. Y. Solid-phase combinatorial synthesis of 1,4-benzoxazin-3(4*H*)-one and 1,4-benzothiazin-3(4*H*)-one derivatives. *Tetrahedron Lett.* **2001**, *42*, 1167-1169.

22. Atkinson, J.; Morand, P.; Amason, J. T.; Niemeyer, H. M.; Bravo, H. R. Analogs of the cyclic hydroxamic acid 2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3-one (DIMBOA): decomposition to benzoxazolinones and reaction with .beta.-mercaptoethanol. *J. Org. Chem.* **1991**, *56*, 1788-1800.

23. Schreder, M. E.; Erker, T. Studies on the chemistry of thienoannelated *O,N*- and *S,N*-containing heterocycles. 17. Preparation of 1*H*-thieno[2,3-b][1,4]thiazine-1-carboxarnides as smooth muscle relaxants. *J. Heterocycl. Chem.* **2000**, *37*, 349-354.

24. Erker, T.; Schreder, M. E.; Studenik, C. Studies on the chemistry of thienoannelated O,N- and S,N-containing heterocycles. Part 19: thieno[2,3-b][1,4]thiazines with calcium antagonistic and potassium opening activities. *Arch. Pharm.* **2000**, *333*, 58-62.

25. Tanaka, A.; Mizuno, H.; Sakurai, M. Preparation of Novel Benzothiophene Derivatives and Their Use as Urokinase Inhibitors. *PCT. Int. Appl.* **1998**, *WO 9811089*.

26. Watanabe, Y.; Osanai, K.; Nishi, T.Synthesis of azido derivatives of semotiadil, a novel 1,4-benzothiazine calcium antagonist, for photoaffinity probes of calcium channels. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1923-1926.

27. Schou, C. S.; Hansen, C. H.; Tagmose, M. T. Synthesis and pharmacological evaluation of 4*H*-1,4-benzothiazine-2-carbonitrile 1,1-dioxide and *N*-(2-cyanomethylsulfonylphenyl)acylamide derivatives as potential activators of ATP sensitive potassium channels*Bioorg. Med. Chem.* **2005**, *13*, 141-155.

28. Omprakash, Ajay, K.; Anil, S. Study of the reaction of chalcone analogs of dehydroacetic acid and *o*-aminothiophenol: synthesis and structure of 1,5-benzothiazepines and 1,4-benzothiazines. *Tetrahedron* **2005**, *61*, 6642-6651.

29. Gao, L.; Rawle, I. H. Analogs of the cyclic hydroxamic acid 2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3-one (DIMBOA): decomposition to benzoxazolinones and reaction with .beta.-mercaptoethanol. *J. Org. Chem.* **2005**, *70*, 9013-9016.

30. John, F. B.; Peter, S.; Timothy, G. Enantiopure 1,4-Benzoxazines via 1,2-Cyclic Sulfamidates. *Synthesis of Levofloxacin, Org. Lett.* **2007**, *9*, 3283-3286.

31. Thomas, G.; John, R. F.; Basil, J. W.; George, V. *Tele* Nucleophilic Aromatic Substitutions in 1-Nitro-3- and 1,3-Dinitro-5-trichloromethylbenzene, and 3-Trichloromethylbenzonitrile. A New Synthesis of the 1,4-Benzothiazine-3(4*H*)-one Ring System from 3-Nitrobenzoic Acid. *Tetrahedron* **2000**, *56*, 447-453.

32. Alessandra, N.; Sofia, M.; Giuseppe, P. A New Insight in the Biosynthesis of Pheomelanins: Characterization of a Labile 1,4-Benzothiazine Intermediate. *J. Org. Chem.* **1999**, *64,* 3009-3011.

33. Alessandra, N.; Paola, D. D.; Giuseppe, P. Characterisation of 1,4-benzothiazine intermediates in the oxidative conversion of 5-*S*-cysteinyldopa to pheomelanins. *Tetrahedron Lett.* **1994**, *35*, 6365-6368.

34. Renata, F.; Fausto, S.; Pilar, U. N. M.; Lara, M.; Cristina, S.; Michela,, R.; Cristina, M.; Carlo, R.4-Benzothiazine analogues and apoptosis: structure–activity relationship. *Bioorg.Med. Chem.* **2003**, *11*, 3245-3254.

ACCEPTED MANUSCRIPT

35. Nazarenko, K. G.; Shtil, N. A.; Chernega, A. N.; Lozinskii, M. O.; Tolmachev, A. A.2-Hetaryl Derivatives of 3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine. *Synthesis* **2004**, 1195-1202.

36. (a) Fokas, D.; Ryan, W.; Casebier, D.; Coffen, D. Solution phase synthesis of a spiro[pyrrolidine-2,3′-oxindole] library via a three component 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett.* **1998**, *39*, 2235–2238; (b) Suchy, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentova, E.Synthesis, Absolute Configuration, and Enantiomeric Enrichment of a Cruciferous Oxindole Phytoalexin, (*S*)-(−)-Spirobrassinin, and Its Oxazoline Analog. *J. Org. Chem.* **2001**, *66*, 3940-3947; (c) Risitano, F.; Grasii, G.; Foti, F.; Nicolo, F.; Condello, M. *Tetrahedron* **2002**, *58*, 191-195; (d) Nair, V.; Biju, A.; Vinod, A.; Suresh, E.Reaction of Huisgen Zwitterion with 1,2-Benzoquinones and Isatins: Expeditious Synthesis of Dihydro-1,2,3-benzoxadiazoles and Spirooxadiazolines. *Org. Lett.* **2005**, *7*, 5139-5142.

37.Nazarenko, K. G.; Shtil, N. A.;Lozinskii, M. O.;Tolmachev, A. A. New 2-functionalized 2*H*-3,4-dihydro-1,4-benzothiazin-3-ones and their application in the synthesis of spiro heterocycles, *Tetrahedron* **2007**, *63*, 7727-7732.

38. Shastri, L. A.; Shivashankar, K.; Kulkarni, M. V. Facile synthesis of some novel 4-{3-aryl-3,4-dihydro-2H-benzo[b][1,4] thiazin-2-yl}-2H-chromen-2-one derivatives, *J. Sulfur Chem.* **2007**, *28*, 625-630.

ACCEPTED MANUSCRIPT

Table 1. Synthesis of 1,4-benzoxazinylcoumarins 10a-10o

Entry	R	R_1	M.P (^oC)	Yield (%)
10a	6-CH_3	H	193	88
10b	6-CH_3	2-Cl	139	86
10c	6-CH_3	4-Cl	253	82
10d	6-CH_3	2-NO_2	223	85
10e	6-CH_3	4-NO_2	202	89
10f	6-CH_3	4-OCH_3	154	84
10g	7-CH_3	H	178	86
10h	7-CH_3	2-Cl	149	85
10i	7-CH_3	4-Cl	215	84
10j	7-CH_3	2-NO_2	233	87
10k	7-CH_3	4-NO_2	261	85
10l	7-CH_3	4-OCH_3	177	86
10m	6-OCH_3	H	188	82
10n	6-OCH_3	2-Cl	226	80
10o	6-OCH_3	4-Cl	153	82

Table 2. Physical data of synthesized compounds **14a-14b** and 1**5a-15b**

Entry	X	R	% Yield	M.P. ^{o}C
14a	O	H	30	128
14b	O	4-Cl	30	137
15a	S	H	35	132
15b	S	4-Cl	36	124

Table 3. Physical and Analytical data of compounds (**17a-17c and 18a-18c**)

Comp.	R	X	Y	M.P (ºC)	Yield (%)
17a	6-CH_3	O	-CH_2	165	73
17b	6-OCH_3	O	-CH_2	152	66
17c	6-CH_3	O	-NCH_2Ph	164	58
18a	6-CH_3	S	-CH_2	135	75
18b	6-OCH_3	S	-CH_2	162	68
18c	6-CH_3	S	-NCH_2Ph	158	65

Table 4. Physical data of compounds (**19a-19b** and **20a-20b)**

Entry	X	Y	% Yield	M.P. ^{o}C
19a	O	-CH_2	30	148
19b	O	-NCH_2Ph	32	153
20a	S	-CH_2	35	132
20b	S	-NCH_2Ph	40	142

Figure 1. R^1=H, R^2=-CH_2OH, R^3=H; R^4=NH-R; a. R^1=H, R^2=-CH_2OH, R^3=NRR; R^4=H

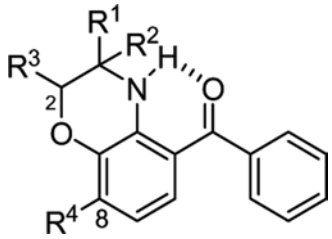


Figure 2

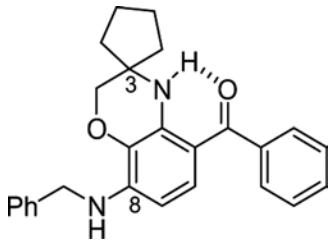
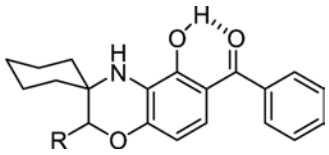


Figure 3. R=OH, NH-R[1]



ACCEPTED MANUSCRIPT

Figure 5

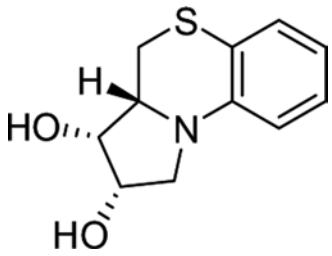
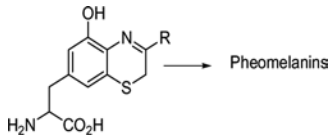
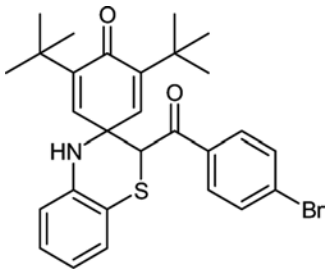


Figure 6



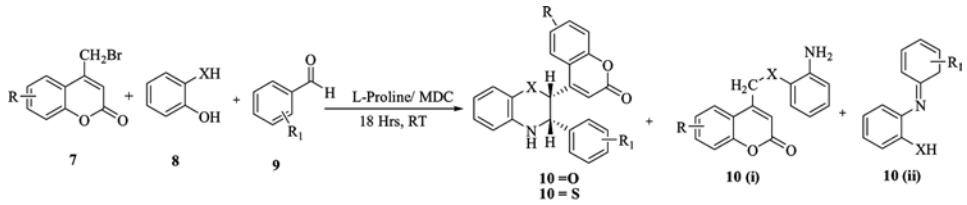
ACCEPTED MANUSCRIPT

Figure 7

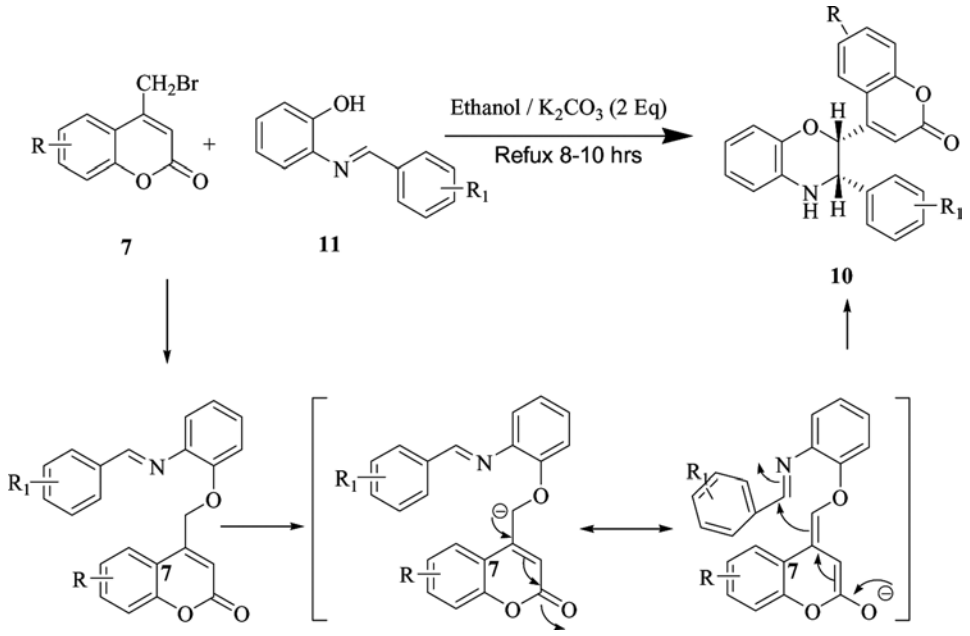


ACCEPTED MANUSCRIPT

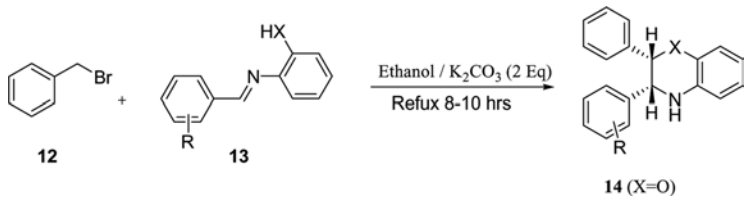
Scheme 1. R=6-CH_3; R_1=H; X=O,S



Scheme 2. R=6-CH_3, 7-CH_3, 6-OCH_3; R_1=H, 2-Cl. 4-Cl, 4-OCH_3, 2-NO_2, 4-NO_2

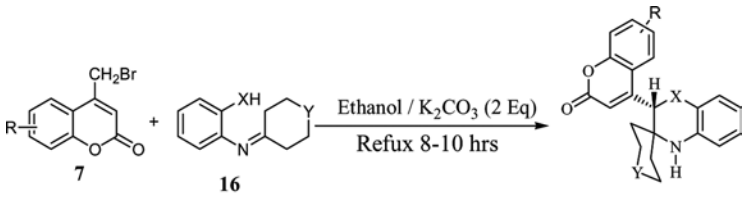


Scheme 3. R=H,4-Cl, X=O and S



12 **13** **14** (X=O)

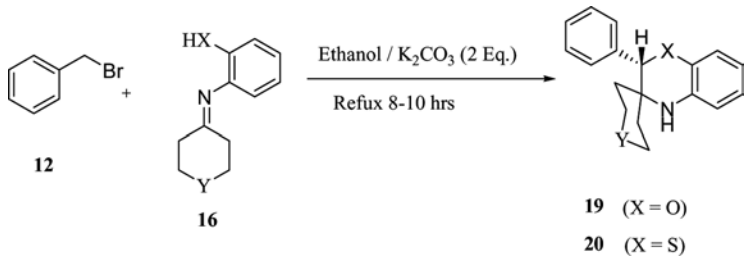
Scheme 4. R=6-CH_3, 6-OCH_3; Y=CH_2, N-CH_2Ph



17 (X = O)

18 (X = S)

Scheme 5. Y=CH_2, N-CH_2Ph



ACCEPTED MANUSCRIPT