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*Article*

# A Highly Efficient Bismuth Salts-Catalyzed Route for the Synthesis of α-Aminophosphonates

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**Abstract:** A convenient synthesis of different types of α-amino phosphonates via one-pot solvent-free three component reactions of aldehydes, amines and phosphites catalyzed by bismuth salts has been investigated. Bismuth triflate is found to be the most effective catalyst for this reaction.

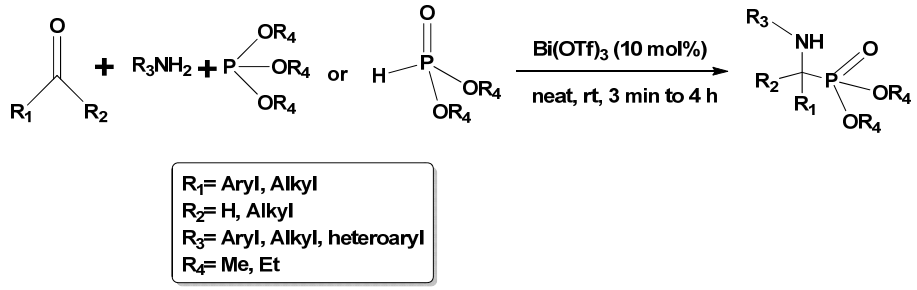
**Keywords:** bismuth salts; catalysis; imines; phosphites; α-aminophosphonates

## 1. Introduction

The synthesis of α-aminophosphonates has received the attention of organic chemists as they represent structural analogues of the important α-amino acids. Various uses of α-amino phosphonates as antimicrobial [1-3], antioxidant [2], antitumor [4-6], antiviral [7] and enzyme inhibitors [8-10] have been discovered. A number of synthetic methods for the construction of α-aminophosphonates have been reported [11] but the nucleophilic addition reaction of phosphites to imines is the most powerful and attractive method. In this context, some catalysts and procedures have been reported such as boric acid [12], silica sulfuric acid [13], magnesium perchlorate [14], titanium dioxide [15], antimony chloride [16], oxalic acid [17], sulfonic acid functionalized ionic liquid [18], hexanesulphonic acid sodium salt [19], zirconium (IV) compounds [20], trifluoroethanol [21], sodium dihydrogen phosphate [22], tetramethyl guanidine [1,3], microwave irradiation [2,7], iron(III) chloride [4] *etc.* In addition, some of the reactions [23-25] are performed in organic solvents.

Recently, bismuth salts have emerged as efficient Lewis acids due to their relatively low toxicity, ready availability at a low cost and tolerance of trace amounts of water. Therefore, we have investigated bismuth salts to address some of the limitations posed by known methods. Herein, in continuation of our research on bismuth salt-catalyzed reactions [26-35], we disclose a novel one-pot synthesis of structurally diverse α-aminophosphonates from aldehydes, amines and di/trialkyl phosphite (Scheme 1). It is also important to mention that we have reported the synthesis of several anticancer compounds using a bismuth salt-catalyzed reaction as the key step [36-45].

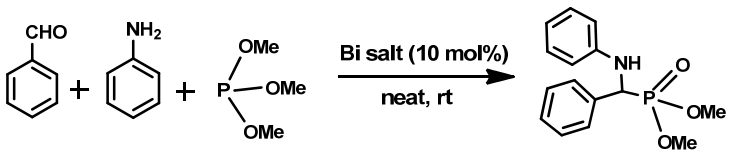
**Scheme 1.** Synthesis of α-aminophosphonates via condensation of amines with carbonyl compounds and di/trialkyl phosphite in presence of bismuth salt as the catalyst.




## 2. Results and Discussion

Reaction of aldehydes with amines results in the formation of imine intermediates which subsequently reacts with di/trialkyl phosphites to produce the corresponding α-aminophosphonates (Scheme 1). A number of bismuth salts (10 mol%) have been screened using the reaction of benzaldehyde, aniline and trimethyl phosphite (equimolar ratio) as a probe. Bismuth triflate proved to be the ideal catalyst (Table 1).

**Table 1.** Bi salts-catalyzed one-pot synthesis of α-aminophosphonates.




| Entry | Bismuth salt (10 mol%) | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | $BiCl_3$ | 2 | 85 |
| 2 | $BiI_3$ | 5 | 75 |
| 3 | $Bi_5O(OH)_9(NO_3)_3$ | 5 | 57 |
| 4 | $BiBr_3$ | 4 | 71 |
| 5 | $Bi(NO_3)_3.5H_2O$ | 5 | 67 |
| 6 | $Bi(OTf)_3$ | 3 min | 98 |

Structurally diverse aldehydes, amines and phosphites were used in the presence of a catalytic amount (10 mol%) of bismuth triflate to afford the corresponding α-aminophosphonates in high to excellent yields (Table 2). Bhattacharya and Kaur reported [46] the synthesis of α-amino phosphonates using bismuth nitrate as the catalyst at room temperature and under microwave irradiation. A very high yield of the product was reported with various substrates. Based on our research on bismuth nitrate-catalyzed reactions [26-35], we are in a position to comment on this paper [46]. Bhattacharya and Kaur claimed to use bismuth nitrate pentahydrate as the catalyst. However, structure of this catalyst as written in this paper indicates that bismuth is monovalent. After careful search of the literature, monovalent bismuth nitrate was not available from any sources. In contrast to their paper, our results with trivalent bismuth nitrate pentahydrate produced α-aminophosphonates in comparatively low yield. Trivalent bismuth halides produced product in better yield than trivalent bismuth nitrate pentahydrate. A comparative study of the catalyst is shown in the Table 1. Aromatic aldehydes gave better yield probably because of the stability of the imines. Conjugated aldehyde produces product in lower yield. The reactions were compatible with different types of functional groups (Table 2).

**Table 2.** Synthesis of α-aminophosphonates via condensation of amines with carbonyl compounds and di/trialkyl phosphite in presence of bismuth triflate (10 mol%) as the catalyst following Scheme 1.

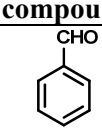
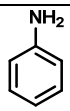
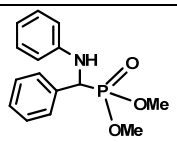
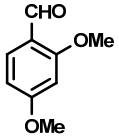
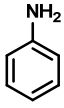
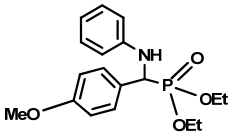
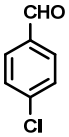
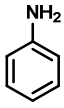
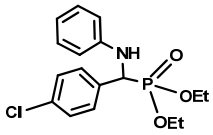
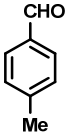
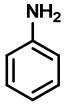
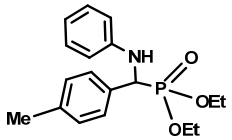
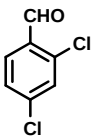
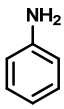
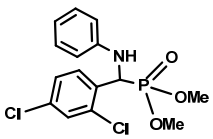
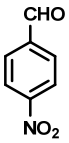
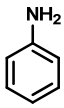
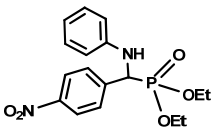
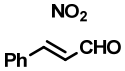
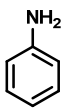
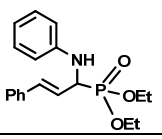
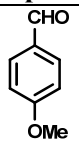
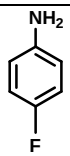
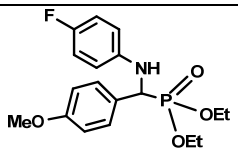
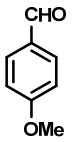
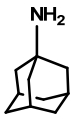
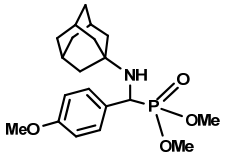
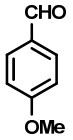
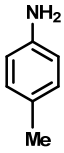
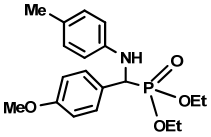
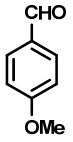
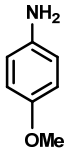
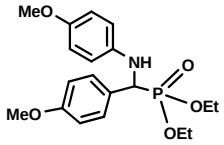
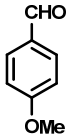
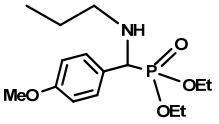
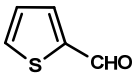
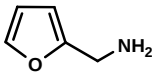
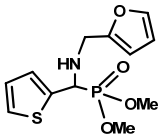
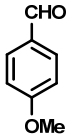
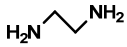
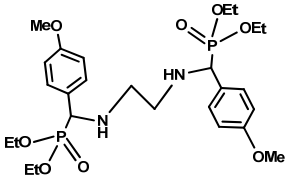
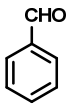
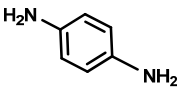
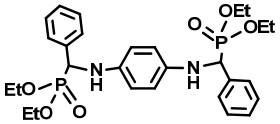
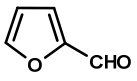
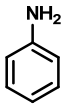
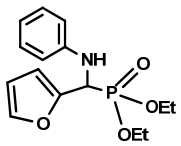
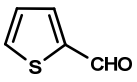
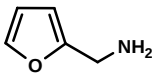
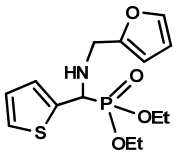
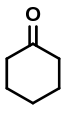
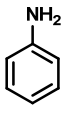
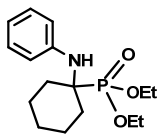
| Entry | Carbonyl compound | Amine | Phosphite | Product | Time (min) | Yield (%)[a] | Ref |
|---|---|---|---|---|---|---|---|
| 1 |  |  | TMP[b] |  | 3 | 98 | 12 |
| 2 |  |  | TEP[c] |  | 10 | 93 | 13 |
| 3 |  |  | DEP[d] |  | 12 | 97 | 15 |
| 4 |  |  | DEP |  | 20 | 94 | 15 |
| 5 |  |  | TMP |  | 15 | 95 | 13 |
| 6 |  |  | DEP |  | 55 | 92 | 15 |
| 7 |  |  | DEP |  | 45 | 74 | 15 |

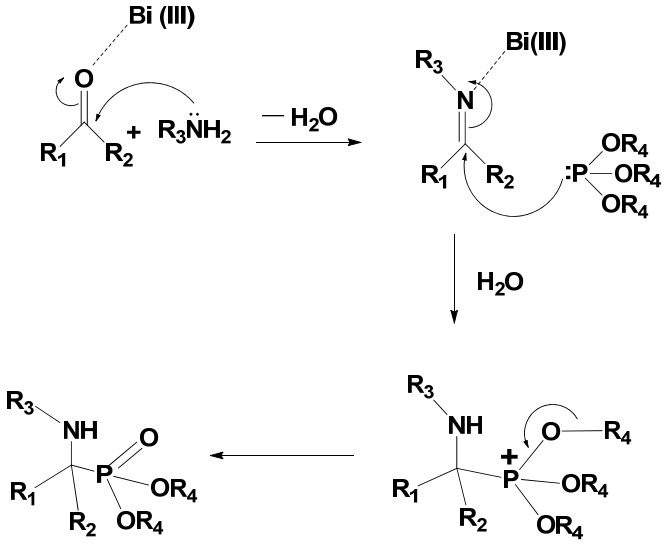
**Table 2.** *Cont.*

| Entry | Carbonyl compound | Amine | Phosphite | Product | Time (min) | Yield (%)[a] | Ref |
|---|---|---|---|---|---|---|---|
| 8 |  |  | DEP |  | 80 | 84 | 15 |
| 9 |  |  | DMP[e] |  | 20 | 95 | 14 |
| 10 |  |  | DEP |  | 90 | 82 | 15 |
| 11 |  |  | DEP |  | 30 | 97 | 15 |
| 12 |  |  | DEP |  | 45 | 89 | 15 |
| 13 |  |  | DMP |  | 40 | 86 | 1 |
| 14 |  |  | DEP |  | 75 | 86 | 15 |
| 15 |  |  | DEP |  | 25 | 91 | 4 |
| 16 |  |  | TMP |  | 15 | 96 | 17 |
| 17 |  |  | DEP |  | 65 | 82 | 1 |
| 18 |  |  | DEP |  | 240 | 72 | 15 |

[a] isolated yield; [b] trimethyl phosphite; [c] triethyl phosphite; [d] diethyl phosphite; [e] dimethyl phosphate.

A plausible mechanism involves the formation of an imine by the addition of aldehyde and amine. It is believed that trivalent bismuth coordinates with the imine nitrogen to accelerate a nucleophilic reaction of phosphite to give a phosphonium intermediate, which then reacts with the water molecule formed during imine formation to yield the final product (Scheme 2).

**Scheme 2.** Plausible mechanistic pathway for the synthesis of α-aminophosphonates.




## 3. Experimental

### *3.1. General*

Melting points were determined in a Fisher Scientific electrochemical Mel-Temp manual melting point apparatus (Model 1001) equipped with a 300 °C thermometer. FT-IR spectra were registered on a Bruker IFS 55 Equinox FTIR spectrophotometer as KBr discs. $^{1}$H-NMR (300 MHz) and $^{13}$C-NMR (75.4 MHz) spectra were obtained at room temperature with JEOL Eclipse-300 equipment using TMS as internal standard and $CDCl_3$ as solvent. Analytical grade chemicals (Sigma-Aldrich incorporation) were used throughout the project. Deionized water was used for the preparation of all aqueous solutions.

*General procedure for the synthesis of α-aminophopsphonates*: Amine (1 mmol) and carbonyl compound (1 mmol) were mixed with di/trialkyl phosphite (1 mmol) in the presence of bismuth triflate (10 mol%). In the case of diamines (Entries 14 and 15, Table 2) the molar ratio of carbonyl compound and phosphite was double with respect to the diamine used. The reaction was monitored by TLC. After the completion of the reaction, dichloromethane (10 mL) was added to the reaction mixture and it was then washed successively with 5% $NaHCO_3$ solution (2 mL) and brine (2 mL). The organic layer was dried with anhydrous sodium sulfate and concentrated. The products were found to be 95% pure from proton NMR study. Pure products were isolated through crystallization (dichloromethane-hexane). No column chromatography was needed for the purification of the products. Compounds obtained from the entries are reported. Our products have demonstrated satisfactory spectral and mp data compared with the reported values.

## 4. Conclusions

In conclusion, bismuth triflate was found to be an efficient catalyst in one-pot reaction of aldehydes, amines, and di/trialkyl phosphite to afford α-aminophosphonates. The main advantages of this method are mild conditions, clean, solvent-free reaction conditions and good to excellent yields. Application of this method toward the synthesis of biologically active molecules is under progress.

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## References

1. Reddy, M.V.N.; Annar, S.; Balakrishna, A.; Reddy, G.C.S.; Reddy, C.S. Tetramethyl guanidine (TMG) catalyzed synthesis of novel α-amino phosphonates by one-pot reaction. *Org. Commun.* **2010**, *3*, 39-44.
2. Rao, A.J.; Rao, P.V.; Rao, V.K.; Mohan, C.; Raju, C.N.; Reddy, C.S. Microwave assisted one-pot synthesis of novel α-aminophosphonates and their biological activity. *Bull. Korean Chem. Soc.* **2010**, *31*, 1863-1868.
3. Reddy, M.V.N.; Kumar, B.S.; Balakrishna, A.; Reddy, C.S.; Nayak, S.K.; Reddy, C.D. One-pot synthesis of novel α-amino phosphonates using tetramethylguanidine as a catalyst. *ARKIVOC* **2007**, *15*, 46-254.
4. Rezaei, Z.; Firouzabadi, H.; Iranpoor, N.; Ghaderi, A.; Jafari, M.R.; Jafari, A.A.; Zare, H.R. Design and one-pot synthesis of α-aminophosphonates and bis(α-aminophosphonates) by iron(III) chloride and cytotoxic activity. *Eur. J. Med. Chem.* **2009**, *44*, 4266-4275.
5. Rao, X.; Song, Z.; He, L. Synthesis and antitumor activity of novel α-aminophosphonates from diterpenic dehydroabietylamine. *Heteroatom Chem.* **2008**, *19*, 512-516.
6. Kraicheva, I.; Bogomilova, A.; Tsacheva, I.; Momekov, G.; Troev, K. Synthesis, NMR characterization and *in vitro* antitumor evaluation of new aminophosphonic acid diesters. *Eur. J. Med. Chem.* **2009**, *44*, 3363-3367.
7. Xu, Y.; Yan, K.; Song, B.; Xu, G.; Yang, S.; Xue, W.; Hu, D.; Lu, P.; Ouyang, G.; Jin, L.; Chen, Z. Synthesis and antiviral bioactivities of α-aminophosphonates containing alkoxyethyl moieties. *Molecules* **2006**, *11*, 666-676.
8. Du, S.; Faiger, H.; Belakhov, V.; Baasov, T. Towards the development of novel antibiotics: synthesis and evaluation of a mechanism-based inhibitor of Kdo8P synthase. *Bioorg. Med. Chem.* **1999**, *7*, 2671-2682.
9. Giannousis, P.P; Bartlett, P.A. Phosphorus amino acid analogues as inhibitors of leucine aminopeptidase. *J. Med. Chem.* **1987**, *30*, 1603-1609.
10. Allen, M.C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J.M. Renin inhibitors. Synthesis of transition-state analog inhibitors containing phosphorus acid derivatives at the scissile bond. *J. Med. Chem.* **1989**, *32*, 1652-1661.

11. Engel, R.; Cohen, J.I. *Synthesis of Carbon-Phosphorus Bonds.* 2nd ed.; CRC Press: Boca Raton, FL, USA, 2003.
12. Karimi-Jaberi, Z.; Amiri, M. One-pot synthesis of α-aminophosphonates catalyzed by boric acid at room temperature. *Heteroatom Chem.* **2010**, *21*, 96-98.
13. Maghsoodlou, M.T.; Khorassani, S.M. Habibi; Hazeri, N.; Rostamizadeh, M.; Sajadikhah, S.S.; Shahkarami, Z.; Maleki, N. An efficient synthesis of α-Amino phosphonates using silica sulfuric acid as a heterogeneous catalyst. *Heteroatom Chem.* **2009**, *20*, 316-318.
14. Bhagat, S.; Chakraborti, A.K. An extremely efficient three-component reaction of aldehydes/ketones, amines, and phosphites (Kabachnik-Fields reaction) for the synthesis of α-aminophosphonates catalyzed by magnesium perchlorate. *J. Org. Chem.* **2007**, *72*, 1263-1270.
15. Hosseini-Sarvari, M. $TiO_2$ as a new and reusable catalyst for one-pot three-component syntheses of α-aminophosphonates in solvent-free conditions. *Tetrahedron* **2008**, *64*, 5459-5466.
16. Ambica; Kumar, S.; Taneja, S.C.; Hundal, M.S.; Kapoor, K.K. One-pot synthesis of α-aminophosphonates catalyzed by antimony trichloride adsorbed on alumina. *Tetrahedron Lett.* **2008**, *49*, 2208-2212.
17. Vahdat, S.M.; Baharfar, R.; Tajbakhsh, M.; Heydari, A.; Baghbanian, S.M.; Khaksar, S. Organocatalytic synthesis of α-hydroxy and α-aminophosphonates. *Tetrahedron Lett.* **2008**, *49*, 6501-6504.
18. Akbari, J.; Heydari, A. A sulfonic acid functionalized ionic liquid as a homogeneous and recyclable catalyst for the one-pot synthesis of α-aminophosphonates. *Tetrahedron Lett.* **2009**, *50*, 4236-4238.
19. Niralwad, K.S.; Shingate, B.B.; Shingare, M.S. Solvent-free sonochemical preparation of α-aminophosphonates catalyzed by 1-hexanesulphonic acid sodium salt. *Ultrasonics Sonochem.* **2010**, *17*, 760-763.
20. Bhagat, S.; Chakraborti, A.K. Zirconium(IV) compounds as efficient catalysts for synthesis of α-aminophosphonates. *J. Org. Chem.* **2008**, *73*, 6029-6032.
21. Heydari, A.; Khaksar, S.; Tajbakhsh, M. Trifluoroethanol as a metal-free, homogeneous and recyclable medium for the efficient one-pot synthesis of α-amino nitriles and α-amino phosphonates. *Tetrahedron Lett.* **2009**, *50*, 77-80.
22. Karimi-Jaberi, Z.; Amiri, M.; Sadeghi, N. Sodium dihydrogen phosphate as an efficient catalyst for one-pot, three-component synthesis of α-aminophosphonates under solvent-free conditions at room temperature. *Synthetic Commun.* **2010**, *40*, 2948-2953.
23. Matveeva, E.D.; Podrugina, T.A.; Prisyazhnoi, M.V.; Rusetskaya, I.N.; Zefirov, N.S. Three-component catalytic method for synthesis of α-amino phosphonates with the use of α-amino acids as amine component. *Russ. Chem. Bull.* **2007**, *56*, 798-805.
24. Matveeva, E.D.; Podrugina, T.A.; Prisyajnoy, M.V.; Zefirov, N.S. Ketones in the catalytic three-component "one-pot" Kabachnik-Fields synthesis of α-amino phosphonates. *Russ. Chem. Bull.* **2006**, *55*, 1209-1214.
25. Matveeva, E.D.; Podrugina, T.A.; Kolesnikova, I.N.; Zefirov, N.S. Benzoylhydrazones in catalytic hydrophosphorylation. *Russ. Chem. Bull.* **2010**, *59*, 411-417.
26. Samajdar, S.; Basu, M.K.; Becker, F.F.; Banik, B.K. Bismuth nitrate-mediated deprotection of oximes. *Synthetic Commun.* **2002**, *32*, 1917-1921.

27. Srivastava, N.; Dasgupta, S.K.; Banik, B.K. A remarkable bismuth nitrate-catalyzed protection of carbonyl compounds. *Tetrahedron Lett.* **2003**, *44*, 1191-1193.
28. Srivastava, N.; Banik, B.K. Bismuth nitrate-catalyzed Versatile Michael reactions. *J. Org. Chem.* **2003**, *68*, 2109-2114.
29. Banik, B.K.; Samajdar, S.; Banik, I.; Ng, S.S.; Hann, J. Montmorillonite impregnated with bismuth nitrate: Microwave-assisted facile nitration of β-lactams. *Heterocycles* **2003**, *61*, 97-100.
30. Banik, B.K.; Adler, D.; Nguyen, P.; Srivastava, N. A new bismuth nitrate-induced stereospecific glycosylation of alcohols. *Heterocycles* **2003**, *61*, 101-104.
31. Banik, B.K.; Banik, I.; Renteria, M.; Dasgupta, S.K. A straightforward highly efficient Paal-Knorr synthesis of pyrroles. *Tetrahedron Lett.* **2005**, *46*, 2643-2645.
32. Banik, B.K.; Garcia, I.; Morales, F.R. Bismuth nitrate-catalyzed Michael reactions of indoles in water. *Heterocycles* **2007**, *71*, 919-924.
33. Bose, A.; Sanjoto, W.P.; Villarreal, S.; Aguilar, H.; Banik, B.K. Novel nitration of estrone by metal nitrates. *Tetrahedron Lett.* **2007**, *48*, 3945-3947.
34. Banik, B.K.; Reddy, A.T.; Datta, A.; Mukhopadhyay, C. Microwave-induced bismuth nitrate-catalyzed synthesis of dihydropyrimidones via Biginelli condensation under solventless conditions. *Tetrahedron Lett.* **2007**, *48*, 7392-7394.
35. Rivera, S.; Bandyopadhyay, D.; Banik, B.K. Facile synthesis of N-substituted pyrroles via microwave-induced bismuth nitrate-catalyzed reaction. *Tetrahedron Lett.* **2009**, *50*, 5445-5448.
36. Becker, F.F.; Banik, B.K. Polycyclic aromatic compounds as anticancer agents: synthesis and biological evaluation of some chrysene derivatives. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2877-2880.
37. Becker, F.F.; Mukhopadhyay, C.; Hackfeld, L.; Banik, I.; Banik, B.K. Polycyclic aromatic compounds as anticancer agents: synthesis and biological evaluation of dibenzofluorene derivatives. *Bioorg. Med. Chem.* **2000**, *8*, 2693-2699.
38. Banik, B.K.; Becker, F.F. Polycyclic aromatic compounds as anticancer agents. 4. Structure-activity relationships of chrysene and pyrene derivatives. *Bioorg. Med. Chem.* **2001**, *9*, 593-605.
39. Banik, B.K.; Becker, F.F. Synthesis, electrophilic substitution and structure-activity relationship studies of polycyclic aromatic compounds towards the development of anticancer agents. *Curr. Med. Chem.* **2001**, *8*, 1513-1533.
40. Banik, B.K.; Becker, F.F.; Banik, I. Synthesis of anticancer β-lactams: Mechanism of action. *Bioorg. Med. Chem.* **2004**, *12*, 2523-2528.
41. Banik, I.; Becker, F.F.; Banik, B.K. Stereoselective Synthesis of β-Lactams with Polyaromatic Imines: Entry to New and Novel Anticancer Agents. *J. Med. Chem.* **2003**, *46*, 12-15.
42. Banik, B.K.; Becker, F.F. Selective anticancer activity of β-lactams derived from polyaromatic compound. *Mol. Med. Reports* **2010**, *3*, 315-316.
43. Banik, B.K.; Samajdar, S.; Becker, F.F. Asymmetric synthesis of anticancer β-lactams via Staudinger reaction. *Mol. Med. Reports* **2010**, *3*, 319-321.
44. Banik, B.K.; Mukhopadhyay, C.; Becker, F.F. Synthesis and biological evaluation of novel dibenzofluorene derivatives as anticancer agents. *Oncol. Lett.* **2010**, *1*, 309-311.
45. Banik, B.K.; Becker, F.F. Novel 6,12-disubstituted chrysene as potent anticancer agent: Synthesis, *in vitro* and *in vivo* study. *Eur. J. Med. Chem.* **2010**, *45*, 4687-4691.

46. Bhattacharya, A.K.; Kaur, T. An efficient one-pot synthesis of α-amino phosphonates catalyzed by bismuth nitrate pentahydrate. *Synlett* **2007**, *5*, 745-748.

*Sample Availability:* Samples of the compounds (mg quantity) are available from the authors.